Racemic and Enantioselective Total Syntheses of Mosquito Oviposition Pheromone from a Naturally Available Unsaturated Fatty Acid

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Abstract

The unnatural *threo*-6-acetoxy-5-hexadecanolide and the natural mosquito oviposition pheromone *erythro*-6-acetoxy-5-hexadecanolide were synthesized in a diastereodivergent fashion in 44% and 33% overall yield respectively from 5-bromovaleric acid and undecanal. The key step utilized a chemoenzymatic epoxidation-lactonization of a naturally available fatty acid to form the 6-hydroxy-5-hexadecanolide core.[17]

The epoxidation strategy was later adapted to allow for an asymmetric synthesis. Shi epoxidation afforded highly enantioenriched (5*R*, 6*R*)-6-hydroxyhexadecanolide (er = 10) in 70 % overall yield. Other derivatives of the chiral ketone catalyst were also screened.

Finally, attempts were made to obtain the correct stereochemistry at C(6) of the target with a dynamic kinetic transformation using lipase and a transfer hydrogenation catalyst. Epimerization of the lactol with the transfer hydrogenation catalyst was successful, but lipase mediated reactions halted at <10 % conversion.

Acknowledgments

Foremost, I would like to take this opportunity to especially thank my graduate supervisor, Prof. Travis Dudding, for allowing me to conduct research as a member of his group, and more importantly providing invaluable guidance throughout the course of this project. I am likewise grateful for the supervision and direction provided by the other members of my advisory committee, Prof. Tomas Hudlicky and Prof. Heather Gordon.

The incentive for this project came about from collaboration with Prof. Dr. Fiona Hunter at Entomogen. I would like to acknowledge Entomogen and NSERC Engage for contributing the monetary funding for this project.

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1.0 Introduction

1.1 Background on Mosquito Oviposition Pheromone

A series of experiments initiated in 1983 by Laurence *et al*. led to the identification of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide [**(-)-1**, Figure 1] as the major chemical component contained within the apical droplets found on egg rafts of *Culex sp.* mosquitos and also responsible for the potent and selective attraction of gravid *Culex* mosquitos.[1] Synthetic Mosquito Oviposition Pheromone (MOP, **(-)-1**) was found to produce a significant dose dependant attractive response, similar to that of egg rafts,[1a] in *Culex sp.* to oviposit (*i.e.*, lay eggs) relative to a control.[1c, e] The examined mosquitos did not exhibit a significant response in oviposition attraction to the (5S, 6R) enantiomer **(+)-1** when compared to a control.[1c, e] The two *threo* enantiomers (5S, 6S) **(+)-2** and (5R, 6R) **(-)-2** also did not show any significant response to oviposition attraction compared to a control.[1c, e] This suggested that the active site interactions occur at the lactone portion of the molecule and were stereoselective at the 5,6-diester portion of the molecule. Alteration of the length of the *n*-alkyl portion of the molecule resulted in a loss of biological activity.[2] More recently it was discovered that the biological response was mediated by an odorant binding protein found in *Culex* antennae.[3a] It was demonstrated that binding occurred through a hydrophobic pocket that could accommodate alkyl chains of all four isomers and hydrogen binding interactions with the chiral hydroxylactone portion of the molecule.[3b] *Aedis sp*. and *Anophelis sp*. mosquitoes did not show a significant response to oviposition attraction, suggesting that the pheromone was genus specific.[6]

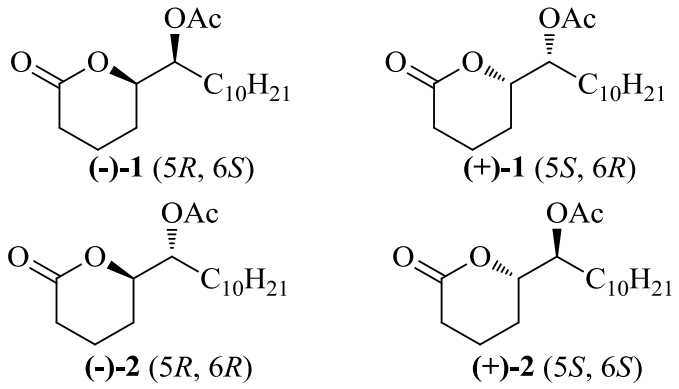


Figure 1. Four Stereoisomers of 6-Acetoxy-5-Hexadecanolide

Culex sp. mosquitoes are vectors for a number of avian and mammalian diseases.[4] Malaria and the West Nile (WN) virus are affecting the agricultural industry and human health significantly in parts of Africa, Asia, Europe and South America.[4] WN virus is a flavivirus disease native to Africa, Asia and Europe that is transmitted in natural cycles between mosquitos and birds but has been known to affect humans and livestock.[4, 5] WN virus was isolated from North American birds as well as *Culex sp*. and *Aedus sp.* mosquitoes in 1999.[4b] The *Culex pipiens* species complex is the predominant vector for WN virus in Europe and North America.[4] *Culex pipiens pipiens* biotype feeds primarily on birds (*i.e.*, ornithophilous), breeds in rural open-air collections of water (*i.e.*, epigeous), requires blood to produce its first batch of eggs (*i.e.*, anautogamous), is unable to breed in confined spaces (*i.e.*, eurygamous) and able to hibernate through the winter (*i.e*., heterodynamous).[4c] In contrast, the *Culex pipiens molestus* biotype is mammophilous, autogamous, stenogamous and homodynamous.[4c] The *Culex quinquefasciatus* species is also a vector for WN virus and shares some common traits with the *Culex pipiens molestus* biotype (*i.e*, stenogamous and homodynamous) and has no preference for birds or mammals, but is found primarily in tropical climates.[4c] The

Culex genus is the primary vector responsible for the spread of WN virus world-wide, and contributes to the spread of other encephalitic diseases as well as parasites.[4, 5] National and international health organizations have implemented programs to monitor the spread of WN virus since its emergence and steady growth of occurrence in Europe and North America.[4a] Although surveillance of mosquito populations is the most accurate means for assessing risk in a given area, sampling mosquito populations remains costly due to the reliance on CO_2 based traps.[4] In order to monitor these diseases, **(-)-1** has become a sought-after attractant for the surveillance of mosquito populations for arboviruses, due to its selectivity for gravid mosquitos (*i.e.*, those carrying fertile eggs) that have had a chance to become laterally infected by taking in blood.[6]

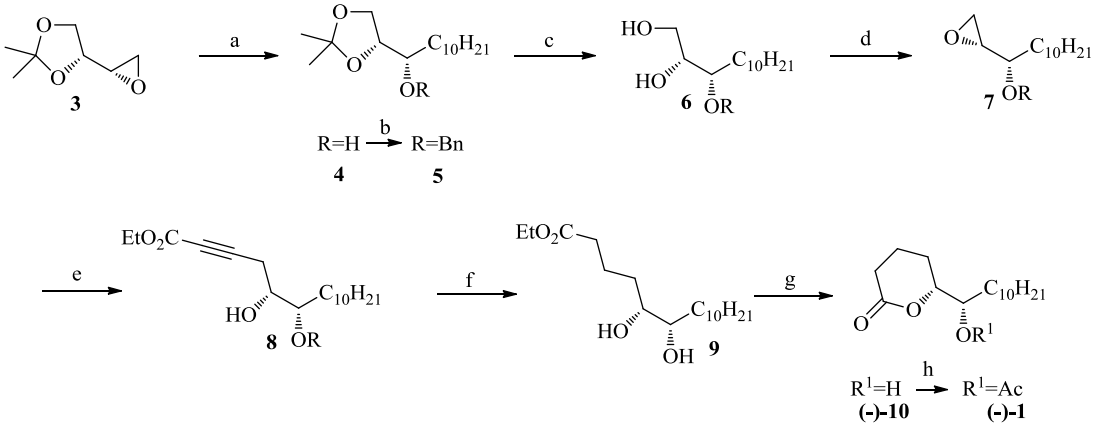
Apart from its use in mosquito surveillance, **(-)-1** has also been used in conjunction with larvacides as an alternative method of pest control.[7] Generally, chiral alkanolides with exocyclic hydroxyl groups are structurally similar to MOP and are gaining importance due to their application as chiral building blocks and their presence within various important natural products.[8d]

1.2 Previous Syntheses

The existing demand for the natural product has generated over twenty total syntheses of **(-)-1** and its corresponding stereoisomers since Mori's total synthesis in 1983.[8, 9, 10, 11, 12a, c] These previous syntheses of 6-acetoxyhexadecan-5-olides have generally revolved around two principal steps: the creation of the requisite carbon skeleton through carbon-carbon coupling reactions and creation of the two chiral centres using chiral pool reagents,[8b, g, h, i, k] Sharpless epoxidation,[1c, 8a, f, j, l, n] asymmetric dihydroxylation,[8d, e] and use of chiral auxiliaries.[8m] Noteably, chiral induction and carbon

framework assembly were combined in a different strategy using asymmetric aldol addition.[10, 11] Among these, brief total syntheses (under 7 steps) of enantioenriched pheromone are much more rare.[10, 8e]

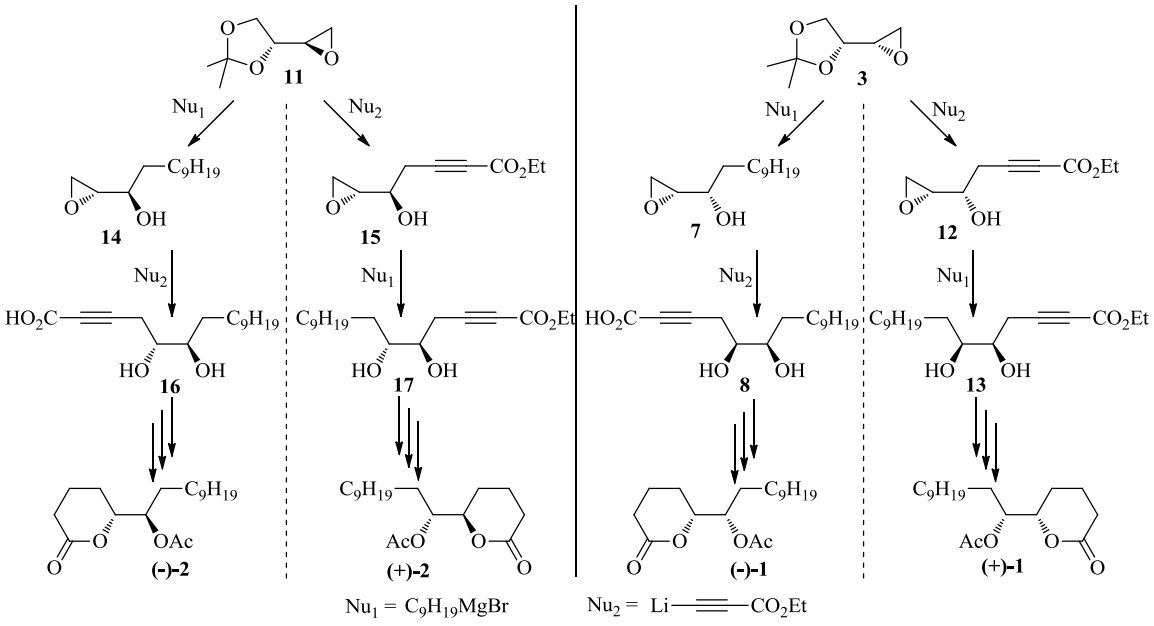
Although enantiomerically pure material was obtained, chiral pool syntheses were often expensive, involving alteration of functionalities in natural products to isolate the requisite chiral centres in the molecule and create reactive sites for coupling reactions to yield the requisite number of carbon atoms. Chiral pool sources have ranged from ascorbic acid,[8g] tartrate,[8b, h] furfuryl alchohols,[8i] and 2-deoxyribose.[8k] Syntheses employed sources of pure enantiomers which were then altered to suit the desired synthetic pathway required to incorporate the chiral source. Notably, Gravier-Pelletier *et al*. employed this strategy by converting D-isoascorbic acid to epoxybutanediol acetonide **3** then proceeding through a nucleophilic alkylative epoxide opening, protection, deprotection, Mitsunobu epoxidation and alkylation sequence to construct the carbon framework with chirality in place (Scheme 1).[8g]



(a) $C_9H_{19}MgBr$, Li_2CuCl_4, THF, -35 °C, 87 % (b) NaH, THF, 50 °C then BnBr, Bu_4NI, 20 °C (c)AcOH/H_2O 4:1, 20 °C, 83 % overall yield **4** to **6** (d) PPh_3, DIAD (diisopropyl azodicarboxylate), 90 °C-130 °C *in vacuo*, 75 %. (e) (*i*) ethyl propiolate, BuLi, THF -80 °C; (*ii*) $BF_3{\cdot}OEt_2$, -100 °C then -80 °C, 87%. (f) H_2 Pd/C, AcOH. (g) (*i*) K_2CO_3, MeOH/H_2O 3:1; (*ii*) HCl; (*iii*) 150 °C, *in vacuo*, 52 % overall yield. (h) Ac_2O, DMAP, 20 °C, 90 %.

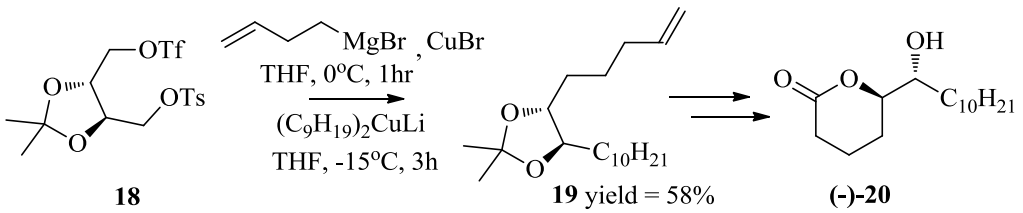
Scheme 1. Enantiopure Synthesis from D- or L-Isoascorbic Acid Derivatives

Subsequent hydrogenation to reduce the internal alkyne and debenzylate at C(6) followed by transesterfication and acetylation yield the MOP **(-)-1**. The (5*S*, 6*S*) **(+)-2** and (5*S*, 6*R*) **(-)-1** stereoisomers were also synthesized by this method by alternating the order of nucleophilic additions to **3** or its epimer **11** (Scheme 2). The above synthesis offers the first example of full characterization of enantiopure forms of each MOP stereoisomer arrived at using a divergent approach.



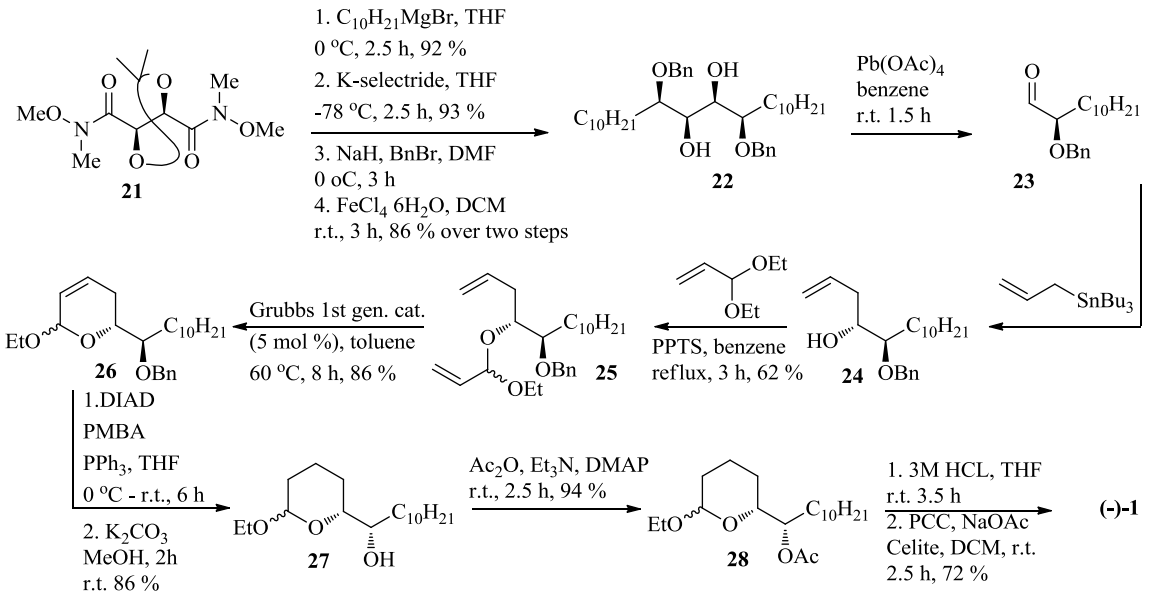
Scheme 2. Divergence by Modulating Alkyl Addition

A similar approach was taken by Kotsuki *et al*. using tartaric acid derivatives by performing a one pot double alkylation to assemble the carbon skeleton (Scheme 3).[8h] A sequence comprising of ozonolysis, oxidation of the aldehyde with $AgNO_3$, deprotection, and acetylation afforded the key (5*R*, 6*R*)-hydroxylactone **(-)-20**, which upon mesylation and acetylation with cesium acetate afforded enantiopure **(-)-1**.



Scheme 3. Enantiopure MOP Synthesis from a Tartaric Acid Derivative *via* One-Pot Dialkylation

More recently, a similar approach was taken where ring closing metathesis (RCM) was used to construct the cyclic portion of the carbon skeleton, starting with a bis-Weinreb amide (**21**) derived from L-tartaric acid to synthesize MOP in eight steps and 31 % overall yield (Scheme 4).[8b] This approach required the same number of steps to complete as Kotsuki's methodology, however two equivalents of **23** were obtained from the starting amide **21** and the use of RCM allowed for an unusual cyclization through carbon-carbon bond formation. Notably, Mitsunobu esterification conditions were used to correct for the relative stereochemistry in this case.



Scheme 4. Synthesis of MOP from Chiral Weinreb Amide using Olefin Metathesis

Asymmetric catalytic methods are advantageous over chiral pool syntheses as they do not rely on stoichiometric amounts of readily available chiral building blocks and instead transfer chirality catalytically to prochiral building blocks. Sharpless asymmetric epoxidation is one asymmetric catalytic strategy that has been employed successfully to introduce chirality in the synthesis of the 6-acetoxyhexadecan-5-olides.[1c, 8a, f, j, l, n] It generally involves the use of titanium(IV)tetraisopropoxide and an ester of either D- or L-tartrate. The two form a dititanium complex with the coordinated tartrate ester imparting asymmetry on the catalyst (Figure 2).[13]

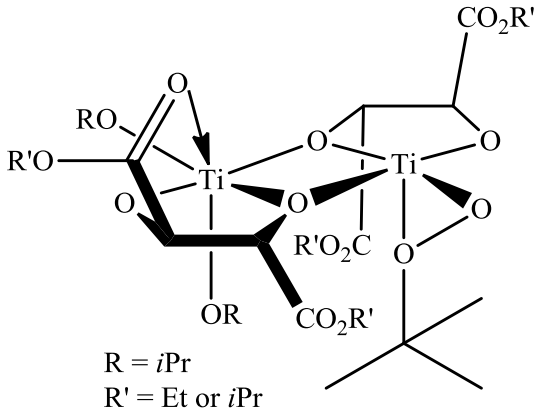


Figure 2. Sharpless Chiral Dimeric Titanium Complex

The catalyst is activated by coordination of *tert*-butyl hydroperoxide and subsequent coordination of the allyl alcohol positions the double bond in a *spiro*-transition state with the coordinated peroxide (Figure 3).[21]

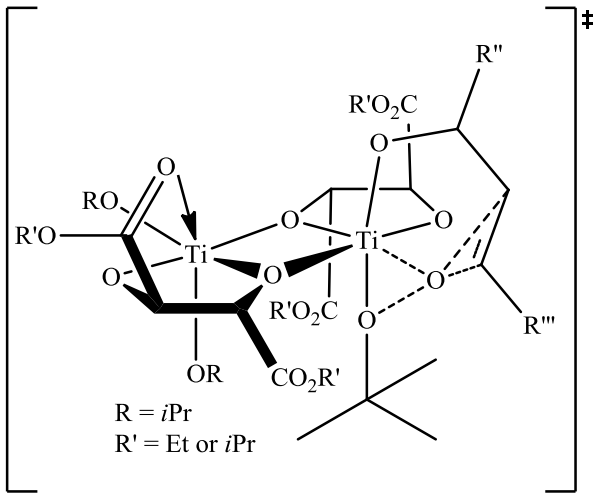
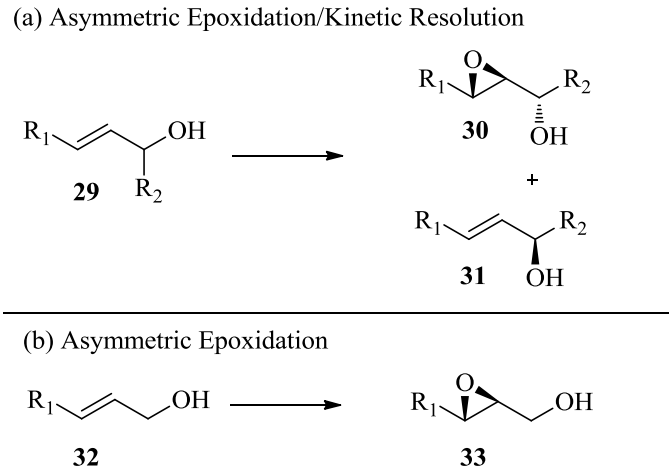


Figure 3. Putative Sharpless Epoxidation Transition State Assembly

Sharpless asymmetric epoxidations are therefore inherently limited to allyl alcohols in substrate scope in order to achieve enantioselectivity. Generally, *cis*-olefins tend to react slower than *trans*-olefins.[13] Apart from these requirements in substrates, Sharpless

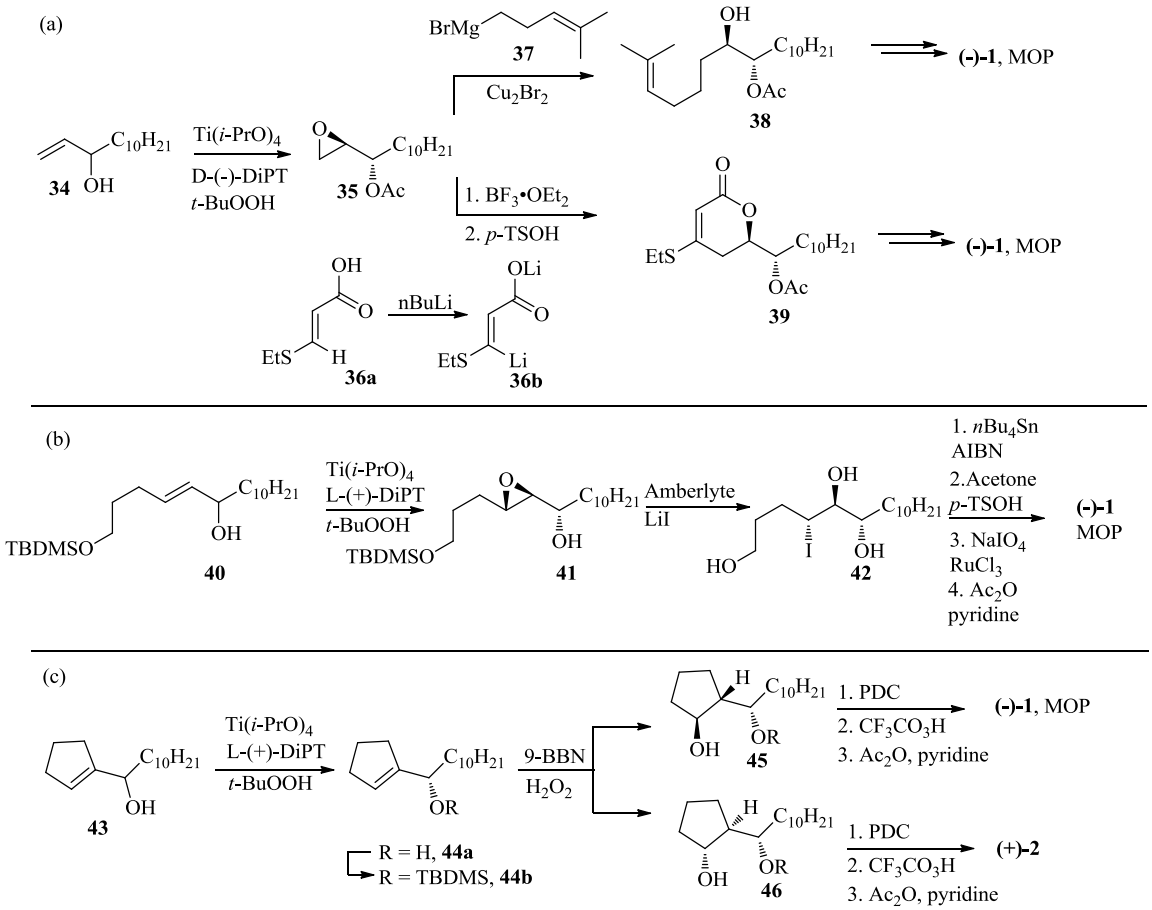
epoxidation is a powerful tool for the synthesis of highly enantioenriched epoxyalcohols and resolution of racemic allyl alcohols to create up to three contiguous chiral centers.

Sharpless epoxidation has been employed in the synthesis of MOP either to resolve secondary alcohols (Scheme 5a),[8a, f, j, l] or epoxidize primary allyl alcohols (Scheme 5b).[8n]



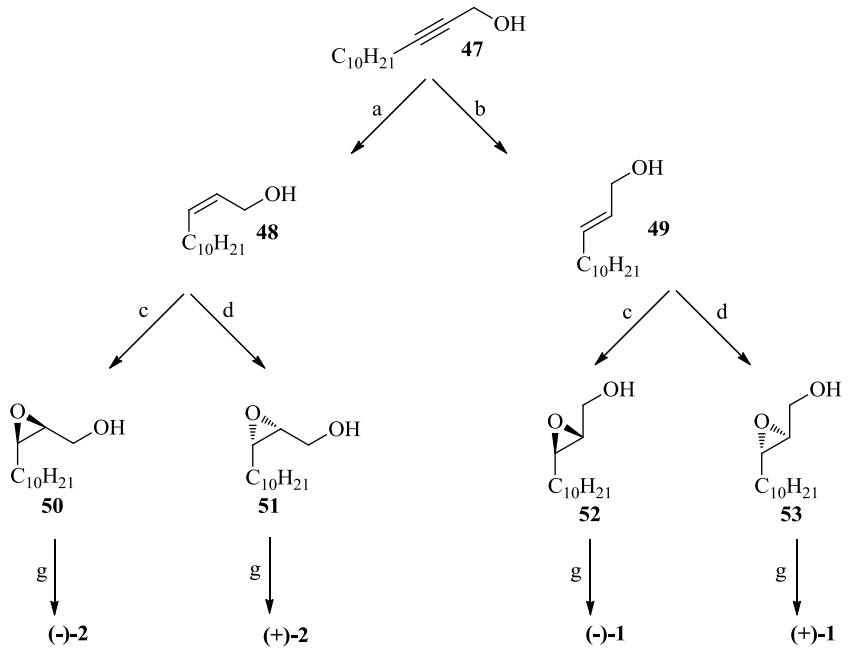
Scheme 5. Strategies for MOP synthesis using Sharpless Epoxidation

In the former case, the chiral secondary epoxyalcohol products of resolution (**30** and **31**) were subjected to nucleophilic epoxide opening to produce the *erythro*-relative stereochemistry with the alcohol oxygen of the starting material on C(6) of the product and the epoxide oxygen on C(5). Epoxide opening proceeded through nucleophilic alkylation (Scheme 6a),[1c, 8l] or simply through nucleophilic opening with iodide once the carbon framework was in place (Scheme 6b).[8f] A third strategy, involved the resolution of a cyclic olefin, **43**, followed by subsequent monoxidation of the unepoxidized olefin, **44a**, then Bayer-Villiger oxidation/deprotection and acetylation to afford MOP **(-)-1** and the corresponding (5*S*, 6*S*)-diastereomer **(+)-2** (Scheme 6c).[8j]



Scheme 6. Different Approaches to MOP Synthesis using Sharpless Epoxidation/Kinetic Resolution

The second strategy, involving the epoxidation of primary allyl alcohols was utilized by Lin *et al*. to produce a stereodivergent synthesis of all four MOP stereoisomers (Scheme 7).[8n]



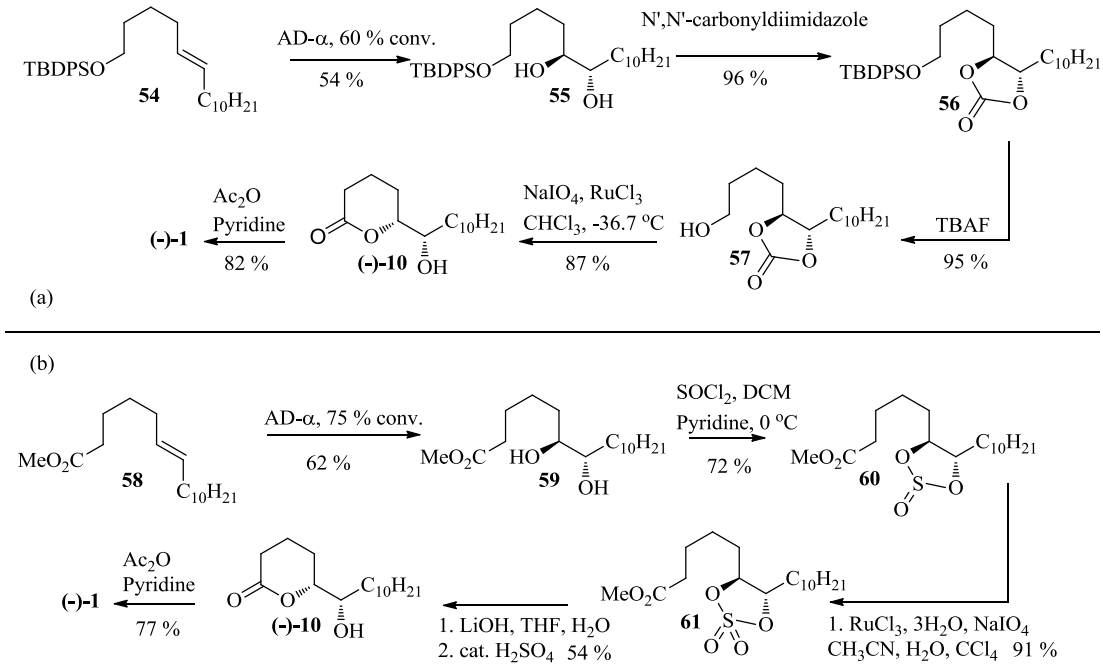
a) LAH-diglyme. b) P-2 Ni, H_2. c) (+)-DET, $Ti(OPr^i)_4$, t-BuOOH, d) (-)-DET, $Ti(OPr^i)_4$, t-BuOOH g) i) CrO_3, Py, CH_2Cl_2 (Collin's reagent); ii) $Ph_3P^+CH_2CH_2CH_2OC(CH_3)_2OCH_3\ Br^-$, NaH, THF, DMSO; iii) AcOH, H_2O/CH_3CN (1:4); iv) Ph_3PRhCl, H_2; v) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (2:2:3); vi) (+)-CSA, CH_2Cl_2; vii) Ac_2O, Py.

Scheme 7. Stereodivergent Synthesis via Sharpless Epoxidation

This approach is entirely divergent, allowing for the synthesis of any desired stereoisomer of MOP from a single starting material. Epoxidation of the primary allyl alcohol has the advantage of theoretically converting the entire starting mass to the desired product, unlike the resolution methods that are limited to 50 % theoretical conversion. However, although the allyl alcohol is required for epoxidation, a series of synthetic steps must be introduced to subsequently obtain the carboxyl terminus of the carbon skeleton.

Asymmetric dihydroxylations on disubstituted alkenes, followed by regiospecific hydroxyl inversion have been successful strategies towards the synthesis of 6-acetoxyhexadecan-5-olides (Scheme 8).[8d, e] Standard Sharpless asymmetric dihydroxylation conditions were employed using AD-α (commercially available mixture of $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, Hydroquinine 1,4-phthalazinediyl diether).

Syntheses involved asymmetric dihydroxylation of a 5-hexadecanoic acid derivative or precursor (**54** or **58**, Scheme 8), followed by protection of the vicinal diol and subsequent formation of the free carboxylic acid followed by concomitant lactonization-deprotection of the diol.

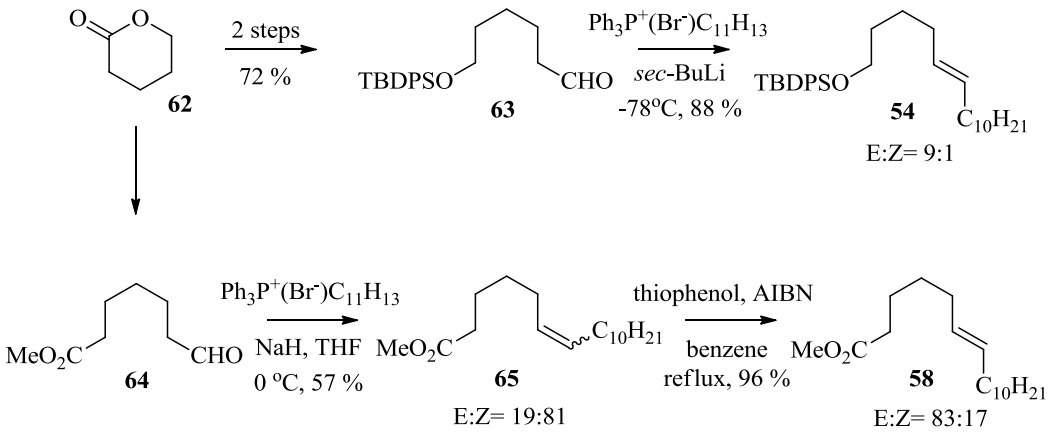


Scheme 8. Two Approaches to MOP Synthesis Using Asymmetric Dihydroxylation

Both syntheses were conceptually similar in their overall design, affording the target **(-)-1** in eight synthetic steps (Scheme 8). As a diol protecting group, N',N'-carbonyldiimidazole (CDI) was the superior reagent (Scheme 8a), allowing for the isolation of **(-)-1** in 22 % overall yield from **54**. Carbonate could be obtained in much higher yield than the analogous cyclic sulfite formed using thionyl chloride (Scheme 8b), resulting in a relatively lower overall yield of **(-)-1** (9 % from **58**). Furthermore, the cyclization step to form lactone **(-)-10** was much more effective, employing a concomitant oxidation/cyclization to obtain the key intermediate in high yield. In

contrast, the two step methyl ester hydrolysis/substitution using LiOH, followed by treatment of the resulting sulfate salt with catalytic sulfuric acid to hydrolyse the sulfate ester resulted in a lower yield of lactone **(-)-1**. It seems likely that elimination by-products of the intermediary sulfate ester would form under the harsh basic conditions used for methyl ester hydrolysis. Nevertheless, the fatty acid methyl ester appeared to be a slightly better substrate for dihydroxylation and represented an advanced intermediate with a potential biological source, however hydrolysis of the methyl ester would not be favourable in later stages of the synthesis (i.e., after oxidation of the olefin).

The fatty acid derivative was arrived at by a Wittig reaction starting from valerolactone derivatives **63** or **64**, with undecyl triphenyl phosphonium bromide (Scheme 9).[8d, e]

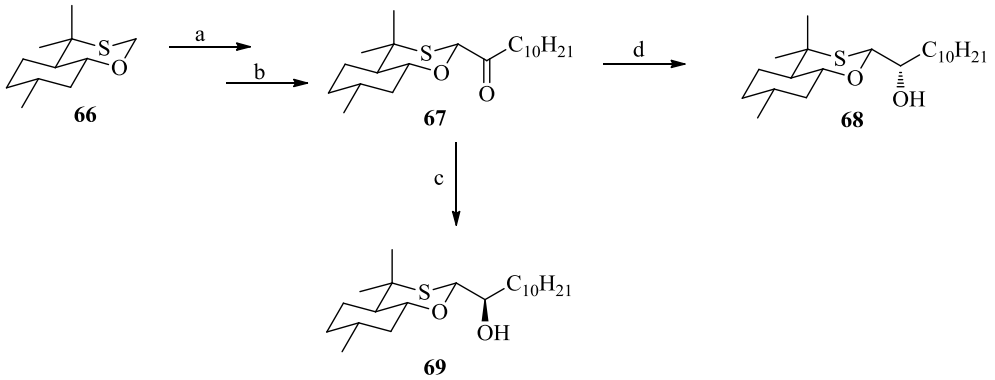


Scheme 9. (*E*)-Selective Fatty Acid Synthesis

The Wittig reaction was controlled using the Schlosser modification to favour the *E*-isomer,[8d] or the favoured *Z*-olefin from a conventional Wittig reaction was isomerized to obtain the *E*-isomer.[8e] The use of *sec*-BuLi base allowed for the formation of the more stable lithiumbetaine, which underwent a subsequent isomerization to the

thermodynamically more stable *trans*-betaine and subsequent formation of oxaphosphetane and collapse to the *E*-olefin, **54**, with aqueous workup in the presence of potassium salts. Conversely, a standard Wittig reaction under kinetic conditions and sodium salts was employed to yield the *Z*-olefin, **66**, followed by radical isomerization using thiophenol and azobisisobutyronitrile (AIBN) to obtain the *E*-isomer **54**.[8e]

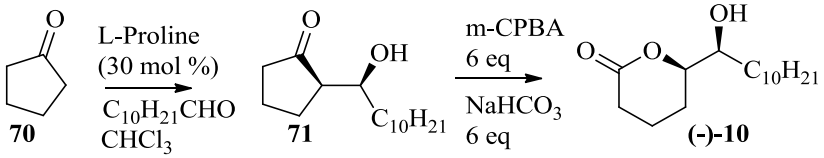
Chiral auxiliaries have been used to induce chirality through steric control of a hydride reduction of a ketone **67** to yield chiral alcohols **68** or **69** (Scheme 10).[8m] The DIBAL-H reduction proceeds in accordance with a Felkin-Anh model to give the (R)-carbinol **69**. The L-Selectride (LiBH(*sec*-Bu)$_3$) reduction with LiI proceeded in accordance to Cram's chelate rule to give the (S)-carbinol **68**. Removal of the chiral auxiliary yielded an α-hydroxy aldehyde. The second chiral centre was created through a stereoselective Grignard addition. Addition with alkyl magnesium bromide in ether was selective for the Cram product with 80% d.e. The *anti*-Cram product of the (*R*)-α-hydroxy aldehyde provided the route to the correct stereochemistry for **(-)-1**.



a) BuLi, $C_{10}H_{21}CHO$. b)CrO_3, pyridine c) DIBAL-H, toluene, -78°C. d) LiBH(*sec*-Bu)$_3$, LiI, toluene, -78°C.

Scheme 10. Chiral Auxiliary Used to Impart Facial Selectivity

Most recently, asymmetric organic catalysis was shown to be an effective approach to all four 6-acetoxyhexadecan-5-olide stereoisomers as well as other chiral lactones with substituted α-hydroxyls.[10, 11] Sun *et al*. first showed that proline-catalyzed aldol additions to cyclopentanone followed by Baeyer-Villiger oxidation with *m*-CPBA to form the δ-lactone are an effective and concise route to 6-hydroxy-hexadecan-5-olide stereoisomers (Scheme 11).[10]

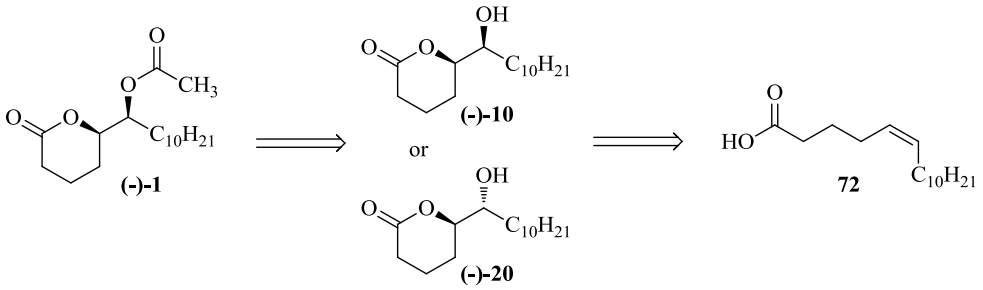


Scheme 11. Synthesis of Enantioenriched Hydroxylactone Intermediate using a L-Proline Catalyzed Aldol Addition

Proline-catalyzed asymmetric aldol additions proceeded through an enamine intermediate derived from a symmetric ketone.[14] The carboxylic acid of the proline portion of the intermediate directs the facial approach of the incoming aldehyde.[14, 15] The absolute geometry of the aldol product is determined by the hydrogen bonding interactions of the aldehyde oxygen with the proline carboxylic acid.[14] The presence of water(~500 mol % H_2O) was demonstrated to invert the diastereochemical outcome of the reaction with respect to anhydrous conditions.[11] The major by-product occured through the transition state with the syn-enamine.[15] The Baeyer-Villiger reaction proceeded through a tetrahedral intermediate following nucleophilic attack of the peracid on the carbonyl carbon of ketone **71**.[16] The tetrahedral intermediate underwent a 1,3-α-carbon migration at the most electron rich carbon while retaining its stereochemistry.[16]

1.3 Racemic Synthesis[17]

Upon closer assessment of previous syntheses, it became apparent that hydroxylactone **(-)-10** or the corresponding (5*R*,6*R*)-diastereomer **(-)-20** occurred as key synthetic intermediates in many previous syntheses (see Schemes 1, 3, 6b, 7, 8, 10, 11 and related references), through which the target **(-)-1** was obtained, often in one step (Scheme 12). Furthermore, the hydroxylactone skeleton was most directly accessed by oxidation of some derivative of fatty acid **72**.

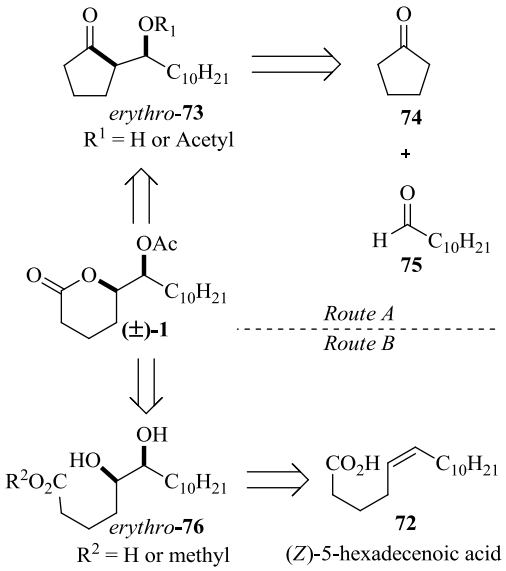


Scheme 12. Retrosynthetic Analysis Based on Previous Syntheses

Although the various enantioselective syntheses have allowed for the elucidation of the specific biological activities of each stereoisomer, these methods have been of limited practicality for large scale production of optically enriched **1** for control or surveillance applications. Notwithstanding, biological activity assays indicated that the non-natural stereoisomers were inactive, but not repulsive,[1c, e] allowing for the use of racemic mixtures **(±)-1** as attractants in oviposition traps.[12] Importantly, it has been shown that bioactive plant oil mixtures containing racemic **(±)-1** were produced from *Kochia scoparia* seed extract that contained ~25 % (*Z*)-5-hexadecenoic acid, thus offering a renewable source for the production of oviposition attractant.[12a, b] Furthermore, rare naturally derived fatty acids are becoming increasingly available through modern

bioproduction technologies. Biosynthetic methods for the synthesis of **72** from palmitic acid, mediated by a desaturase enzyme in mutant *E. coli* strains have recently been reported,[18] while different mutant strains of yeast or *E. coli* have been used to produce various unsaturated fatty acids in industry.[19]

The most successful strategies for the synthesis of racemate **(±)-1** have involved either aldol addition of cyclopentanone to undecylaldehyde followed by Bayer-Villiger oxidation and acetylation (Route A, Scheme 13),[9] or dihydroxylation of (*Z*)-5-hexadecenoic acid (**72**) or the methyl ester of **72** followed by intramolecular cyclization to form the *erythro*-hydroxyalkanolide precursor to **(±)-1** (Route B, Scheme 13).[12a, c]

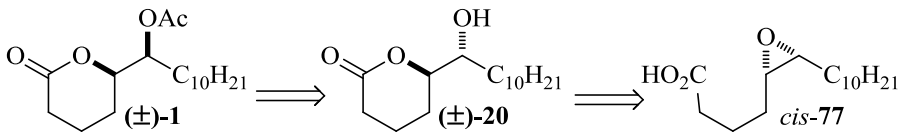


Scheme 13. Effective Racemic Strategies

Both strategies lead to a concise synthesis of racemic *erythro*-6-acetoxy-5-hexadecanolide [**(±)-1**] with high overall yields (~ 65 %). Utilizing route B, product **(±)-1** was obtained from the naturally available acid **72** *via* the dihydroxylation route; unfortunately this transformation required the use of stoichiometric heavy metal reagents.

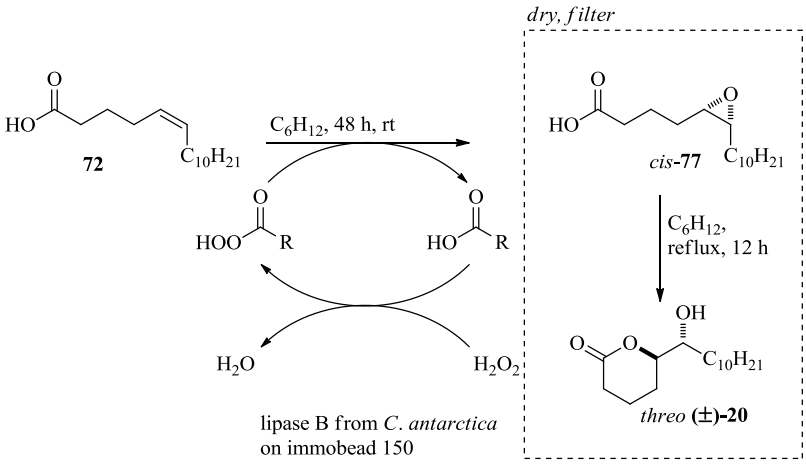
Alternatively, route A was recently employed to access enantioenriched **(-)-1** and **(-)-2** using the Hajos-Parish asymmetric aldol reaction;[10, 11] however, the large excess of *m*-CPBA (~ 5 eq) for Bayer-Villiger oxidation detracted from this procedure. Apart from the hazardous reagents required for these oxidations, the necessity for purification by column chromatography at each step of the synthesis greatly limited the scalability of these reactions.

To overcome the limitations associated with the above oxidations and at the same time incorporate salient features of routes A and B in Scheme 13, it was reasoned that a more ideal synthesis would intersect with a naturally available acid **72** intermediate and proceed through a benign, metal-free oxidation. Epoxidations of olefins, mediated by the *in situ* lipase catalyzed generation of peroxyacids using aqueous hydrogen peroxide as a primary oxidant have been reported in the literature and would offer one means to this end.[20] It was also understood that this very mild oxidation procedure would yield the hydroxylactone **(±)-20**, after which the relative geometry at C(6) could be inverted by esterification to afford **(±)-1** (Scheme 14).



Scheme 14. Racemic Retrosynthetic Analysis

Accordingly, the total synthesis of racemate **(±)-1** *via* an environmentally benign lipase mediated epoxidation of (*Z*)-5-hexadecenoic acid **72** is reported in the first section of this work (Scheme 15).



Scheme 15. Chemoenzymatic Epoxidation/Lactonization

Marked features of this synthesis include the minimization of column purification by using urea inclusion crystallization and favourable 'Green' metrics.

1.4 Asymmetric Synthesis using Shi Epoxidation

Having established a sound racemic synthesis, catalytic methods for the chiral epoxidation of fatty acid **72** were explored. Nevertheless, the lack of functionality near the alkene made **72** a difficult substrate for chiral oxidation. Although some success had been reported with Sharpless asymmetric dihydroxylation of methyl esters of **72,** reactions had to be stopped at low conversions (60-70 %) and required a difficult cyclization procedure to obtain the correct diastereomer.[8d, e] Previous syntheses employing chiral epoxidation relied on earlier introduction of chirality, followed by carbon-carbon bond formation to obtain the requisite carbon skeleton, at the cost of extra synthetic manipulations (*vide supra*). To avoid the introduction of additional synthetic steps, and as an extension of the initial strategy to proceed through fatty acid intermediate

72, the direct asymmetric epoxidation of this unfunctionalized alkene was then investigated.

The most widely used methods for olefin epoxidation have generally relied on the presence of so-called "handles" near the alkene to transfer asymmetry from the catalyst to the substrate. The most common substrates for alkene epoxidation have therefore been allyl alcohols as in Sharpless epoxidation,[13] and aryl substituted alkenes as in Jacobsen epoxidation.[21] Both of the above techniques rely on the oxidation of a transition metal center (i.e., Ti, W, Mo, Mn) by a primary oxidant and creation of a bias for the transition state assembly leading to the favoured stereochemistry of the epoxide using a chiral ligand.

Methods for asymmetric epoxidation of unfunctionalized olefins have been limited to date.[22] Apart from biocatalytic approaches utilizing chloroperoxidase enzymes,[23] or P450 monooxygenases in whole-cell fermentations,[24] organocatalytic epoxidation techniques have had moderate to high success in terms of yield and enantioselectivity for unfunctionalized olefins, such as monounsaturated fatty acids.[25] Asymmetric organocatalytic approaches have relied primarily on the use of chiral organic acids in the presence of primary oxidants, or dioxiranes generated *in situ* from chiral ketones.[25] The latter have had generally more success with regard to enantioselectivity. However more recently, more sophisticated chiral organic acid catalysts such as **81** have been used in conjunction with lipase and hydrogen peroxide to generate a chiral peroxy-acid *in situ*, leading to modest enantioselectivities for various phenyl-substituted styrenes (Figure 4).[27]

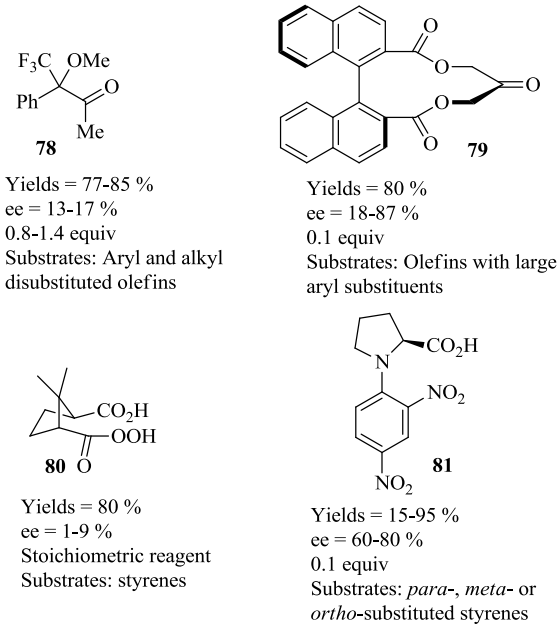


Figure 4. Organic Auxiliaries and Catalysts for Asymmetric Epoxidation of Olefins

Nevertheless, early iterations of chiral ketone catalysts struggled with low selectivities (5-20 % ee) and required near stoichiometric catalyst loadings.[28, 29] These problems were found to arise from two sources, the epimerization of α-carbonyl carbons leading to erosion of enantioselectivity, and the competitive Bayer-Villiger oxidation of ketones to esters leading to degradation of the catalyst. Over the years increasingly sophisticated catalyst designs have managed to overcome epimerization problems by incorporating chiral α-quaternary carbons into the structure of the catalyst, or by employing axially chiral backbones (i.e., BINOL), although the latter approaches have been less successful.[29] The competitive Bayer-Villiger oxidation products can be partially limited through careful control of reaction conditions to favour the dioxirane product (*vide infra*).

Between 1996 and 2006, Shi and coworkers reported a variety of carbohydrate derived chiral ketone catalysts with chiral α-*spiro* functionalities and success with the epoxidation of olefins with various substitutions and functionalities (Figure 5).[29b-d]

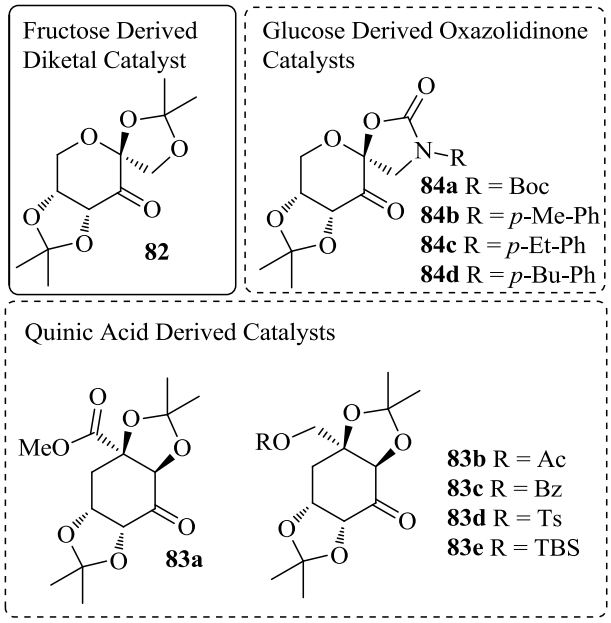
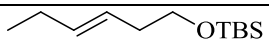
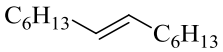
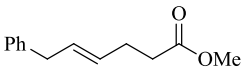
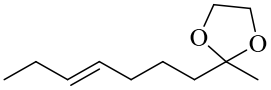
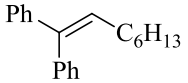
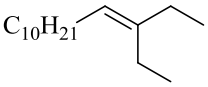
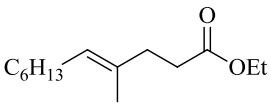
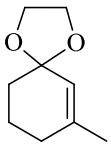
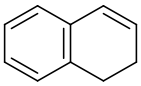
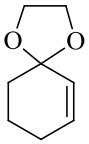
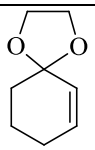
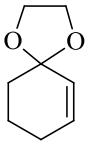
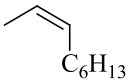
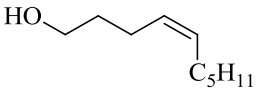
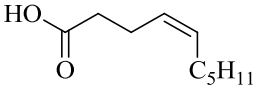
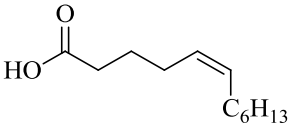


Figure 5. Classes of Shi's Catalysts and Examples of Common Derivatives

Impressive enantioselectivities were observed for a variety of *trans*- and trisubstituted olefins using ketone **82**, which features a quaternary spiroketal functionality at the α-position and a fused ketal blocking the bottom face of the main ring (Entries 1-8, Table 1).[30, 31]

Table 1. Asymmetric Epoxidation of Olefins using Shi's Ketone Catalysts

Entry	Catalyst	Loading	Substrate	Yield (%)	ee (%)	Absolute Configuration
1	**82**	0.3		75	93	(+)-R,R
2	**82**	0.2		88	93	(+)-R,R
3	**82**	0.3		76	91	(+)-R,R
4	**82**	0.3		92	92	(+)-R,R
5	**82**	0.3		66	94	(+)-R
6	**82**	0.3		94	89	(+)-R

7	**82**	0.3		91	84	(+)-R,R
8	**82**	0.3		41	97	(+)-R,R
9	**82**	0.3		92	12	(+)-R,R
10	**82**	0.3		43	61	(+)-R,R
11	**82**	0.3		90	24	(-)-R
12	**83b**	0.1		78	68	(+)-R,R
13	**83b**	0.05		90	65	(-)-R
14	**84a**	0.3		61	97	(+)-R,R
15	**84a**	0.15		92	81	(-)-R
16	**84d**	0.25		52	64	-
17	**84d**	0.25		89	82	-
18	**84d**	0.25		75	91	RR-lactone
19	**84d**	0.25		85	86	RR-lactone

Initially stoichiometric quantities of ketone **82** were required to maintain high enantioselectivity due to the degradation of catalyst *via* the competitive Bayer-Villiger oxidation of the ketone.[31] Upon careful screening of solvent, pH and temperature parameters, it was found that the competitive oxidation pathways can be disfavoured at

high pH and low temperature and polar aprotic solvents, thereby reducing catalyst loading to 20-30 mol %.[31, 32] The catalyst was later found to effectively mediate the epoxidation of silylenol ethers, esters, conjugated enynes and conjugated dienes with moderate to high enantio-, chemo- and regioselectivity.[33] While high enantioselectivities were obtained with disubstituted *trans* and trisubstituted alkenes, *cis* and terminal alkenes were converted with high yield but low enantioselectivites in reactions catalyzed by ketone **82** (Entries 9-11, Table 1).[31]

A series of second generation pseudo-C_2 symmetric catalysts **83a-e,** derived from (-)-quinic acid, were later developed, moreover **83b** was found to provide improved enantioselectivities with *cis*-disubstituted and terminal olefins (Entries 12 and 13, Table 1).[34] Although some success was had with this class of catalyst, the lengthy synthesis (9-10 steps) detracted from this approach. The initial success of the pseudo-C_2 symmetric catalysts initiated a series of studies focused on probing the catalyst structure with an aim to develop an effective catalyst for the epoxidation of *cis* and terminal olefins.[34b, 35]

With no further success on variants of the two previous motifs, *spiro* or fused acetonide rings were replaced with *N*-substituted oxazolidinones, of which class **84** had significant success with the epoxidation of a variety of *cis*-disubstituted and terminal olefins (Entries 14-19, Table 1).[36] Notably, Shi and coworkers, in their recent work, were able to epoxidize a C_{12} fatty acid (yield = 78 %, ee = 88 %) using a derivative of their chiral ketone epoxidation catalyst **84d** (Entry 19, Table 1).[37] Epoxidation of hydroxyalkyl and methyl substituted olefins resulted in lower enantioselectivity (Entry 16 and 17, Table 1), while increasing alkyl chain length (R = Me, Et, *n*-Bu) led to increased enantioselectivity.[37c] The authors proposed that stereoinduction was governed by

hydrophobic interaction of the substrate alkyl chain with the *para*-substituted anilino portion of the catalyst and aqueous solvation of the substrate carboxylate in **TS1**, based on the observed selectivity trends and previous theoretical work on dioxirane olefin epoxidation (Figure 6).[38]

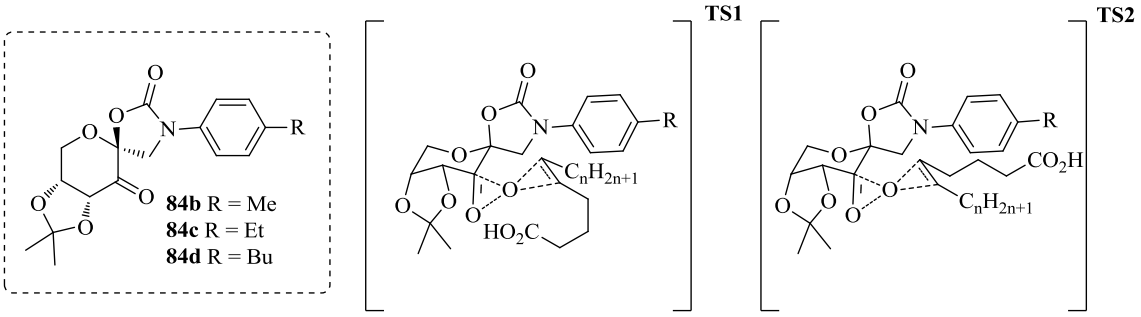
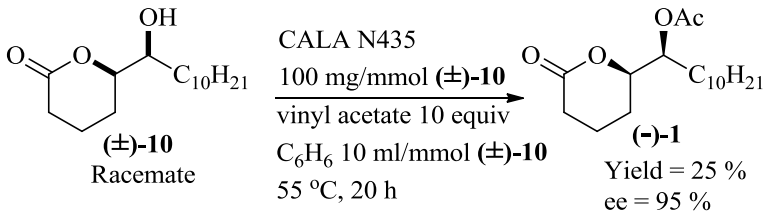


Figure 6. Shi's Epoxidation Catalysts and Proposed Competing *Spiro*-Transition States

The synthesis of **(-)-1** was attempted by means of chiral epoxidation of **72**, to investigate this mode of stereoinduction while providing an example of a four step, asymmetric synthesis of MOP that intersects fatty acid **72**.

1.5 Dynamic Kinetic Transformation Experiments

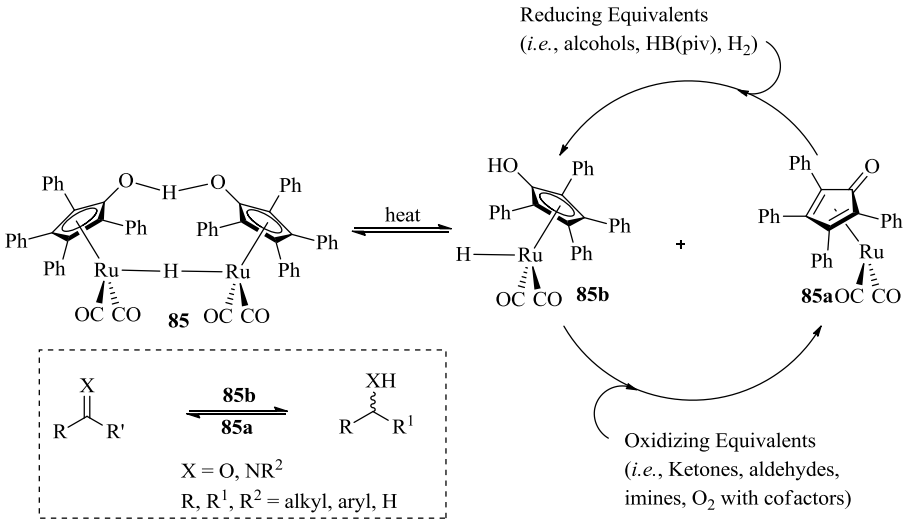
Although asymmetric epoxidation afforded the hydroxylactone skeleton in fairly high optical purity, the problems associated with esterification and epimerization of C(6) remained unaddressed. It was known that the resolution of racemic mixtures of *erythro*-hydroxylactone **(±)-10** using immobilized *Candida antarctica* lipase A(CALA) and vinyl acetate in anhydrous media to yield MOP in high enantiopurity had been reported (Scheme 16).[39]



Scheme 16. Kinetic Resolution of *erythro*-Hydroxylactone ((±)-10)

This work provided the preliminary evidence of selectivity for the target stereoisomer using CALA, however the relative stereochemistry of the (5*R*,6*R*)-hydroxylactone **(±)-20** would have to be adjusted for a lipase-mediated approach to be feasible in this system. It was also known that Bäckvall and coworkers had demonstrated that the dynamic kinetic resolution of secondary alcohols could be accomplished by incorporating a process by which the alcohol was racemized, namely the *in situ* oxidation-reduction mediated by a dimeric ruthenium catalyst, to achieve full conversion of the starting racemic alcohol.[40]

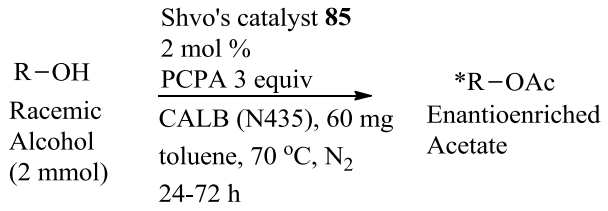
The synthesis of the dimeric ruthenium complex and the reductive and oxidative properties of the basic and acid monomers formed in solution were first reported by Shvo and coworkers.[41] The complex was demonstrated to be an effective redox catalyst for the oxidation of amines and secondary alcohols or reduction of ketones and imines (Scheme 17).[42]

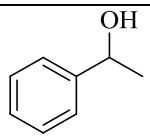
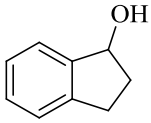
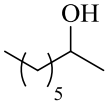
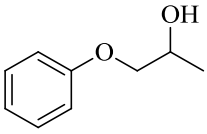
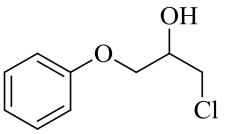


Scheme 17. Shvo's Diruthenium Complex as a Redox Catalyst

A series of enantioenriched esters were synthesized from racemic secondary alcohols using Shvo's catalyst **85**, *C. antarctica* lipase B (CALB), and *p*-chlorophenyl acetate (PCPA) as an acyl donor (Table 2).[40]

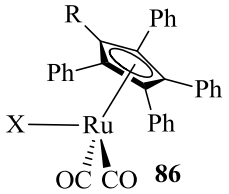
Table 2. Backvall's Dynamic Kinetic Resolution of Secondary Alcohols



Entry	Alcohol	Yield of Acetate (%)	ee (%)
1		80	99
2		77	99
3		80	97
4		88	99
5		68	79

All alkyl and aryl substituted secondary alcohols with large differences in steric bulk between substituents were resolved with high yield and optical purity except for the α-chloroalcohol (entry 5, Table 2). The reduced yield and enantiopurity are likely a result of

increased steric crowding of the alcohol, making it a poor nucleophile for the dissociation of the acyl-lipase complex. This steric effect appears from this example to be forgiving, as modest yield and optical purity were obtained nonetheless. Subsequently, monomeric forms of the catalyst were developed (**86**, Figure 7), allowing for reactions to be conducted at room temperature using *t*BuOK (5 mol %) as an activator, since heat activated dissociation was not required in this case.[43]

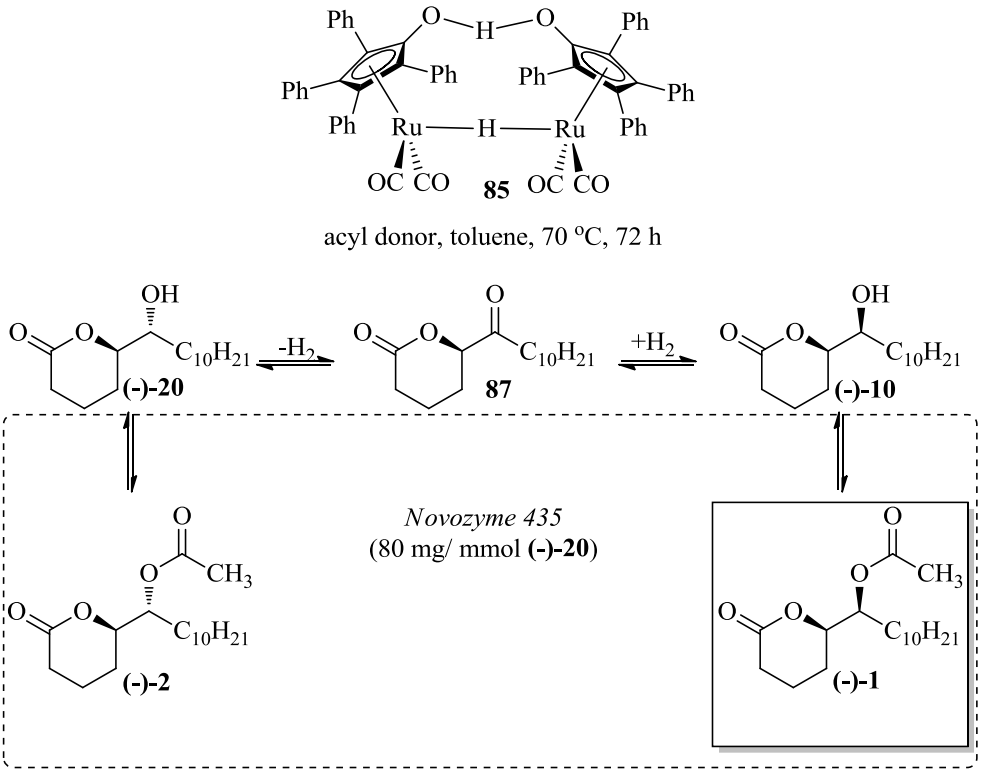


86

X = Cl, Br, I
R = Ph, Me

Figure 7. Monomeric Ruthenium Catalyst

The lower temperature allowed for reduced lipase loadings (3 mg/mmol), which degraded slowly at elevated temperatures. Although CALA was selective for **(-)-10** in a resolution of *syn*-hydroxylactones **(±)-10**, there was no evidence concerning the selectivity between the acetylation of (5*R*, 6*R*)-**(-)-20** and (5*R*, 6*S*)-**(-)-10** alcohols. The transformation of **(-)-20** to MOP [**(-)-1**] using Shvo's catalyst and immobilized lipases [*i.e.*, Novozyme 435 (N435, CALB) and Immobead 150 (CALA or CALB)] was therefore investigated in this work (Scheme 18).

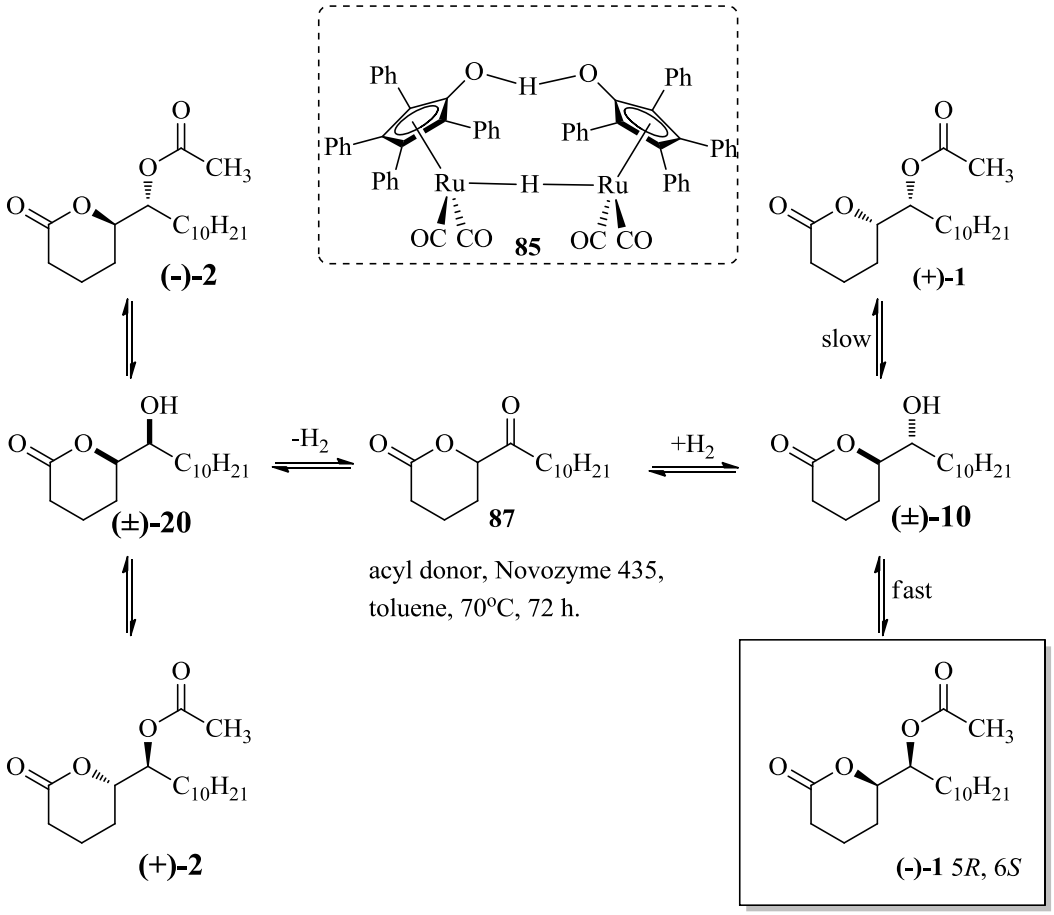


Scheme 18. Dynamic Kinetic Transformation Strategy for Enantioenriched (5*R*, 6*R*)-Hydroxylactone ((-)-20)

The epimerization of the C(5) center was a concern, but it was thought that under the anhydrous conditions, the relative rate of hydrolysis and intramolecular lactonization should be too slow to allow for the accumulation of long-lived lactone-open forms of **(-)-20**. Similarly, the acetylation of the C(5) position was of little concern as the intramolecular re-lactonization was more likely to be preferred.

Furthermore, with evidence for the dynamic asymmetric transformation of a racemic mixture of 1,3-diol enantiomers and diastereomers to form a single enantiomer of the diacetate using a modification of Bäckvall's procedure for secondary alcohols,[44] the transformation of the racemic *anti*-hydroxylactone **(±)-20** was also investigated.

Although 1,3-acyl migration would occur in the 1,3-system,[44] it was reasoned that the 1,2-monoester diol **(±)-20** would not be able to undergo such a transformation. This approach would be the most favorable if successful, as the costly synthesis of the asymmetric organocatalysts **84b-d** could be avoided and may provide an asymmetric route to each of the four stereoisomers of MOP simultaneously (Scheme 19).

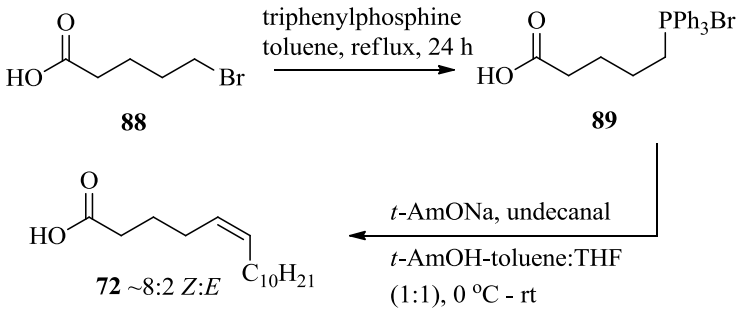


Scheme 19. Dynamic Kinetic Transformation Strategy for Racemic *threo*-Hydroxylactone ((±)-20)

2.0 Results and Discussion

2.1 Synthesis of Racemate[17]

At the outset, fatty acid **72** was synthesized by Wittig olefination under kinetic conditions to favour the (*Z*)-isomer (Scheme 20), as determined by characteristic signals from ^{1}H and ^{13}C NMR.[45] Although Wittig olefination cannot be considered green, the reaction was chosen as a facile route to pure 5-hexadecenoic acid **72**, as a proof of principle for the synthesis of **(±)-1** from the naturally available fatty acid.



Scheme 20. Synthesis of Fatty Acid Intermediate

While investigating choice of base, it was found that the use of sodium *t*-amyloxide (*t*-AmONa), in a similar manner to that described by Dauben *et al.*,[46] resulted in higher yields and cleaner workup than analogous reactions with potassium *t*-butoxide in THF (see Appendix A1.1 for a detailed experimental procedure)(Table 3).

Table 3. Choice of Base and Purification Technique in Wittig Olefination

Entry	Base	Solvent	Urea Yield (%)[a]	Column Yield (%)[b]	*Z*:*E*[c]
1	t-BuOK	THF	32	45	8:2
2	t-AmONa	THF: toluene (1:1)	74	-	8:2

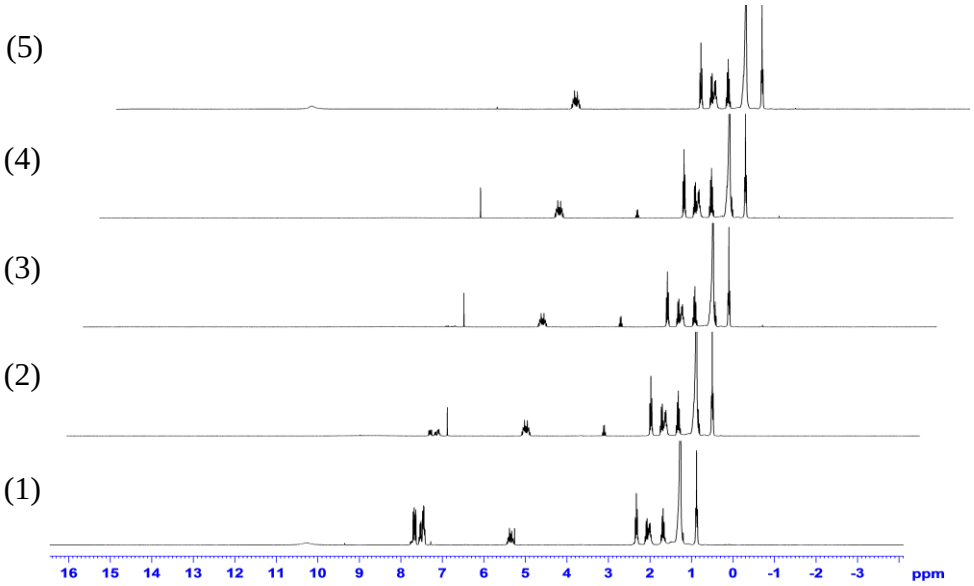
(a) Yield of reactions purified using two serial urea inclusion crystallizations at 5 g scale. (b) Yields of reactions purified by column chromatography at 100 mg scale. (c) Ratios were estimated using ^{1}H NMR.[45]

Purification methods for the removal of triphenylphosphine oxide (TPPO) were then investigated. The majority of TPPO remained in the organic reaction medium, however ~25 % of TPPO was carried over in the acid/base extraction resulting in a significant TPPO impurity in the crude oil extract. The use of column purification proved challenging, requiring a gradient mobile phase starting with hexanes, then hexanes-ethyl acetate (1:1), to produce colourless fatty acid in 61 % yield at a maximum 100 mg scale. To overcome difficulties with large scale column purification, the gram scale (1 – 5 g) purification of extract was achieved using urea inclusion crystallization.[47] The urea purification process involved the crystallization of urea in a solution of fatty acid in methanol. The fatty acid was retained in the solid urea while impurities remained in the solution. The solid urea was collected by filtration and purified fatty acid was obtained by dissolving the crystals in dilute HCl (1 M) and extracting with Et_2O. Using the conditions outlined by Swern and Parker for the purification of oleic acid from vegetable oil,[47] the

purification of the crude fatty material obtained from acid-base extraction from the Wittig reaction mixture was attempted. Under the initial conditions, fatty acid was successfully obtained after four purifications with 65 % mass recovery overall (Entry 1, Table 4; Figure 8).

Table 4. Conditions for Purification of Crude Fatty Acid using Urea Crystallization

Entry	Mass of crude fatty acid (g)	[Urea] (M)	Relative volume (ml/g)	No. Steps	Mass recovery (%)
1	1.0	6.6	9	4	65
2	1.0	12	9	8	63
3	1.0	3.3	9	4	48
4	1.0	6.6	13	2	80



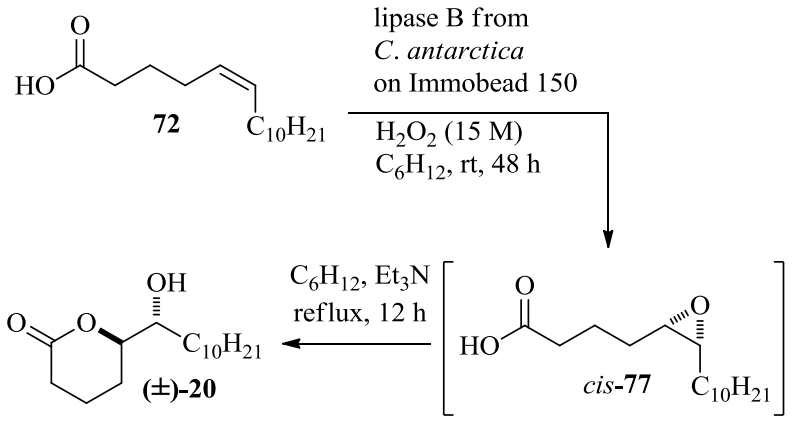
Bottom to top: 1H NMR spectra of (1) crude fatty acid material obtained from acid-base extraction of Wittig reaction mixture, (2-4) fatty acid material obtained from urea crystallization, and (5) the pure fatty acid obtained from a fourth purification step.

Figure 8. ^{1}H NMR Spectra of Fatty Acid Material Obtained from Serial Purifications with Urea

Increasing the concentration of the urea solution resulted in greater recovery but lower selectivity for the fatty acid (Entry 2, Table 4), while the inverse effect was observed for more dilute solutions (Entry 3, Table 4). Improved conditions were generated by using a larger volume of urea solution at the concentration described by Swern and Parker relative to the weight of crude oil material. It was found that washing the filter cake containing retained fatty acid in urea with hexane resulted in cleaner material without loss of recovery. Inclusion crystallization with urea under these conditions allowed for the isolation of up to 3 g of clear colourless fatty acid material that was free of TPPO and analytically pure in 74 % overall yield and retention of the (*Z*)-stereochemistry, while

producing only aqueous urea solution and a small volume of TPPO in methanol as waste (Entry 4, Table 4).

With the requisite fatty acid in hand, the lipase-mediated Prilezhaev oxidation of the olefin was investigated (Scheme 21).



Scheme 21. One-Pot Lipase Mediated Prylazhaev Epoxidation/Cyclization

Initially, the incremental addition of hydrogen peroxide to a 100 mM solution of fatty acid **72** in cyclohexane over immobilized lipase resulted in a poor combined yield (30 %) of hydroxylactone and epoxyacid (Entry 1, Table 5). Previously, it was reported that the epoxyacid **77** undergoes oxidation to the peracid at a much slower rate than the unsaturated acid **72**, while the formation of peracid is much faster than the epoxidation.[20a] Accordingly, it was reasoned that an incremental addition of the fatty acid would maintain higher concentrations of the unsaturated fatty acid **72** during the progress of the reaction, which ultimately resulted in complete consumption of fatty acid as observed by TLC after 48 hours with minimal formation of by-products (Entry 2, Table 5).The epoxidation led to the formation of epoxy acid **77** with ~10 % hydroxylactone **(±)-20** as observed by crude ^{1}H NMR. Thereafter, complete lactonization was observed by heating

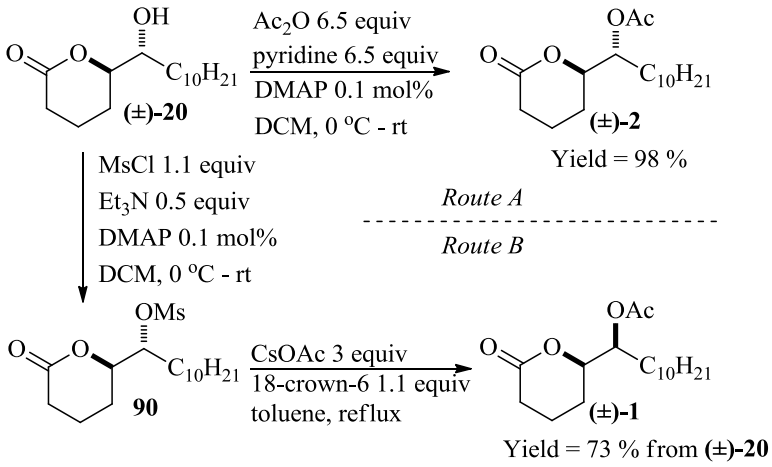
the cyclohexane solution under reflux. Further optimization revealed that the addition of 0.04 % (v/v) Et_3N significantly reduced the time required for lactonization from 72 h to 12 h, likely due to the base acting as a proton shuttle. The diastereomerically pure *threo*-hydroxylactone **(±)-20** was isolated in 40 % yield by crystallization from hexanes, and the remaining hydroxylactone **(±)-20** was obtained from flash chromatography of the mother liquor and subsequent crystallization for a combined yield of 65 %. With these working experimental conditions, the ability to reuse the immobilized lipase was investigated. It was found that the procedure could be repeated up to three times with no apparent loss of activity, so long as reaction runs were repeated immediately after filtration (Entry 2-4, Table 5). Storage of the used immobilized lipase for one week at 7 ^{o}C resulted in complete loss of activity. Using a different immobilizing product such as N435 did not have any significant impact on yield.

Table 5. Oxidation Conditions and Catalyst Recycling

Entry	Addition time (h)[(a)]	Aliquots of fatty acid 72	No. of lipase reuses[(c)]	Yield (%)[(d)]
1	24	1	0	30
2	24	4	0	69
3	24	4	1	68
4	24	4	2	69

(a) Aqueous H_2O_2 (15 M) was added over 24 h via syringe pump. (b) Aliquots of a solution of **72** (0.21 M) in cyclohexane were added to the reaction in 6 h increments. (c) Fatty acid **72** (1.5 mmol) was epoxidized over 48 h using the same 126 mg of lipase (CALB Immobead 150) for each reuse. (d) Represents yield of hydroxylactone **(±)-20**.

The synthesis was completed by way of a late diastereodivergent acetylation strategy. To this end, the *threo*-**(±)-2** was synthesized by *O*-acetylation of **(±)-20** using standard conditions (Scheme 22, Route A).[11] Conversely, **(±)-1** was synthesized by mesylation of the C(6) hydroxyl, followed by substitution of the resulting mesylate with acetate (Scheme 5, Route B).[8h]



Scheme 22. Diastereodivergent Acetylation Strategy

At this stage, the reaction metrics of the key oxidation steps and the overall synthesis, including several commonly used green metrics,[48] were estimated for this synthesis and compared with two of the more successful racemic syntheses (see Appendix A3.0 for raw data used to calculate metrics).[8h, 11] Considering that current 'Green' metrics fail to account for every possible parameter that influences the environmental impact of a process, no one metric can be applied to assess the sustainability of a given process. As such, a series of green metrics were estimated, along with standard reaction metrics like yield and steps, to compare the presented racemic synthesis with successful syntheses from the literature. Two metrics relating to mass efficiency were selected; (1) Sheldon's E-factor was selected as an easy measure of

relative waste and (2) Glaxo-Smith-Klein's (GSK) metric was used to gauge reaction mass efficiency (RME). Carbon efficiency (CE) was also calculated to gauge the efficiency of the transfer of organic material in this synthesis. The E-Factor and RME were calculated for each step of the synthesis by Equations 1 and 2 respectively, where m_{sm} is the mass of starting materials and m_p is the mass products.[48]

$$E = \frac{m_{sm} - m_p}{m_p} \qquad \textbf{Equation 1.}$$

$$RME = \frac{m_p}{m_{sm}} \times 100\% \qquad \textbf{Equation 2.}$$

The masses of all consumable starting reagents and catalysts were incorporated, while solvents were considered recoverable and aqueous solutions were considered benign, and therefore excluded from the calculation. These assumptions were made for the sake of comparing syntheses at the bench scale, where solvent choices, quantities and lifecycles can be expected to change significantly during scale up to an industrial process. Silica and urea were considered recoverable and were not factored into the equation. CE was determined according to Equation 3, where n_p is the moles of product, n_{sm} is the moles of each reagent, C_{sm} is the number of carbons of that reagent and C_p is the number of carbons in the product.

$$CE = \frac{n_p \times C_p}{\sum C_{sm} \times n_{sm}} \times 100\% \qquad \textbf{Equation 3.}$$

The reaction and green metrics of this reaction were then compared with those of the previous successful conventional syntheses.[9, 12c] Analysis of the reaction metrics for the key oxidation step (Scheme 21 and Table 5, Entry 4) revealed that the lipase mediated reaction was more efficient in terms of mass efficiency despite its lower yield when

compared to oxidation with osmium and potassium ferricyanide (Table 6). Although the dihydroxylation proceeded with high carbon efficiency, the use of excess inorganic salts lowered its RME and increased its E-factor significantly. Meanwhile, Bayer-Villiger (BV) oxidation had a greater reaction mass efficiency and E-factor but lower carbon efficiency due to the stoichiometric organic reagent. Lipase mediated epoxidation, although somewhat lacking in yield and RME with respect to BV oxidation, was more carbon efficient than BV oxidation and had a lower E-factor than both. More importantly, toxic transition metal reagents or *m*-CPBA were replaced with aqueous hydrogen peroxide in the lipase approach. Although cyclohexane was used as a solvent, it was successfully recovered by distillation (~ 95 % recovery), and reused in subsequent reaction runs.

Table 6. Comparison of Oxidation Reaction Metrics

Metric	**Dawson *et al.*[9]**	**Michaelakis *et al.*[12c]**	**This Work**
Yield of **(±)-20**	82 %	90 %	69 %
Oxidant	*m*-CPBA	$K_3Fe(CN)_6$	H_2O_2
E-Factor	1.3	15.1	0.4
RME	44 %	6.2 %	66 %
CE	55 %	92 %	69 %

Values reported for this work were calculated from reaction parameters obtained from a representative epoxidation reaction, yields for this oxidation were generally reproducible within ± 5 %. Values for previous work were calculated from data reported in experimental sections of the work in question.

Finally, the E-factor for the overall process was determined as a sum of E-Factors at each step, while the overall RME and CE was calculated as the product of each RME and CE in the linear sequence. The overall synthesis scored lower in comparison to the oxidation alone (Table 7). Although the overall synthesis was more mass and carbon efficient than that proposed by Michaelakis *et al*., overall yields were comparable to the other two syntheses. The synthesis of Dawson *et al*. was the most mass and carbon efficient among the three. However, the nature of reagents and reaction conditions cannot be accounted for by the available green metrics. As such, metrics can only serve to aid in a qualitative assessment of the relative sustainability of different processes or reactions when placed into the context of what is known about the environmental impact of the different reagents used in the respective processes or reactions.

Table 7. Comparison of Overall Synthesis Metrics

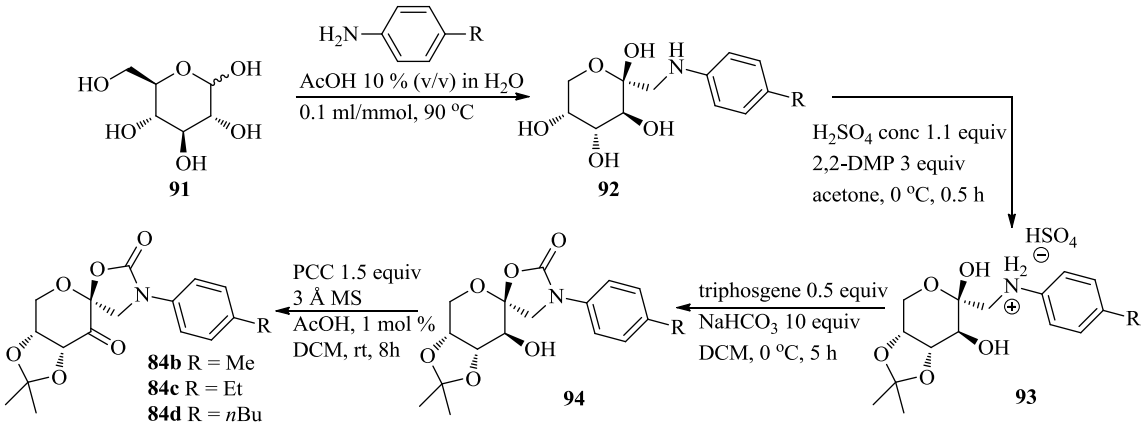
Metric	**Dawson *et al*.**[6]	**Michaelakis *et al*.**[9c]	**This Work**
Yield[(a)]	22 %	23 %	16 %
Steps	3	5	4
E-Factor	6	106	9
RME	5.2 %	0.0020 %	2.1 %
CE	12 %	0.047 %	3.5 %

(a) Represents the overall yield of the active (5*R*,6*S*)-**(-)-1** in a mixture of stereoisomers

2.2 Shi Epoxidation

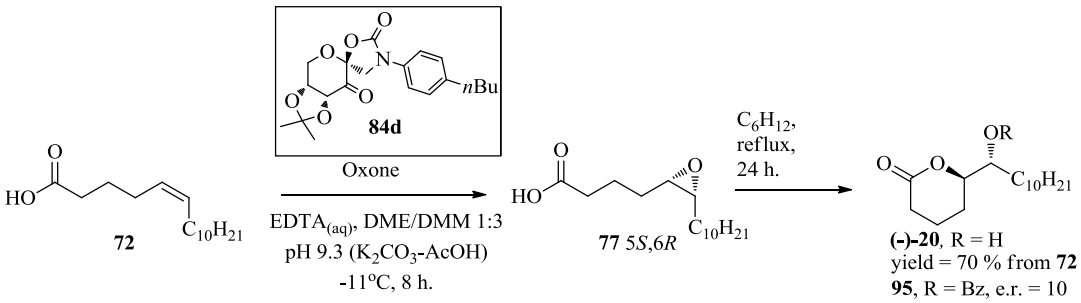
Shi's catalysts (**84b-d**) were synthesized using a combination of the two published syntheses (Scheme 23).[37a, b] Recrystallization of **92** from ethanol/ether was

absolutely necessary to obtain even modest yields in subsequent steps. TEMPO/bleach oxidation of **94** consistently resulted in poor conversion (~45 % by recovered starting material) and products were difficult to isolate and purify resulting in low overall yields of < 25 %. Oxidation using PCC was somewhat more successful with yields ranging between 55-57 % obtained quite reproducibly.[37a]



Scheme 23. Synthesis of Shi's catalysts

Under Shi epoxidation conditions, the fatty acid **72** was epoxidized and partially lactonized, resulting in an approximate 60:40 mixture of epoxide **77** and hydroxylactone **(-)-20** which were isolated together (Scheme 24). Subsequently, the mixture was heated to reflux in cyclohexane to convert residual **77** to lactone **(-)-20**. Interestingly, no proton transfer catalyst (Et_3N) was required to aid in the lactonization step when crude reaction extract from Shi's epoxidation was heated in cyclohexane under reflux. Prior purification of the epoxidation products by flash chromatography followed by lactonization resulted in a similarly slow lactonization requiring a catalytic amount of Et_3N to promote lactonization. This suggested that Shi's catalyst or one of its degradation products may aid in catalysis of the lactonization step.



Scheme 24. Chiral epoxidation and lactonization

Reactions catalyzed by **84b-d** converted olefin to the key lactol intermediate, **(-)-20**, with similar overall yields (65 % - 70 %), however optical activity increased with increasing alkyl chain length of the catalyst (Table 8). The enantiomeric ratio was estimated for the most optically active product by HPLC analysis of the benzoyl ester of hydroxylactone **(-)-20** as the ratio of the relative peak areas at 254 nm.

Table 8. Yield and Enantioselectivity of Asymmetric Epoxidation/Lactonization using Different Epoxidation Catalyst Derivatives

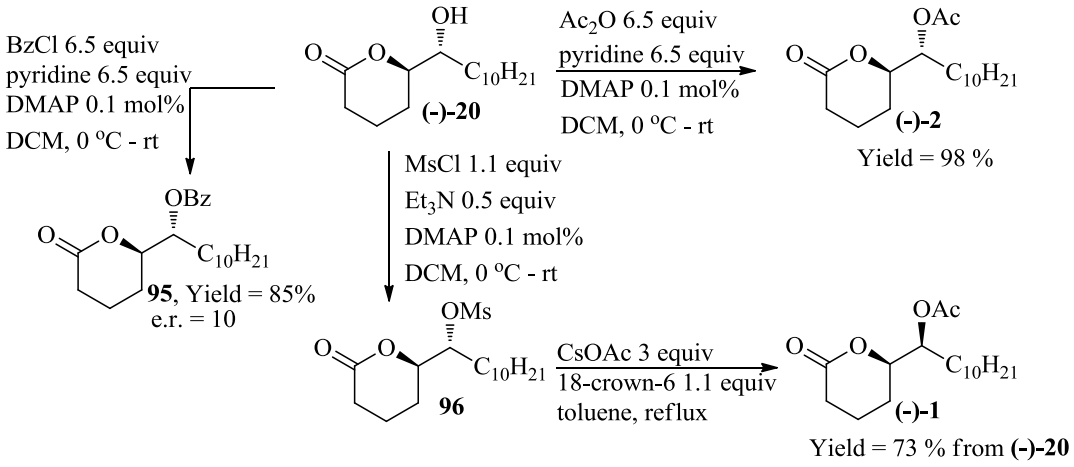
Entry	Catalyst (Figure 5)	Yield (%)[a]	$[\alpha]_D$ (conc. g/100ml)[b]	e.r.[c]	Absolute Configuration[d],[8g]
1	**84b**	65	-6.5(1.01)	-	(-)-R,R
2	**84c**	68	-8.3(1.04)	-	(-)-R,R
3	**84d**	70	-9.3(0.95)	10:1	(-)-R,R

(a) Represents the isolated yield of **(-)-20** and the corresponding enantiomer **(+)-20**. (b) Optical rotation was obtained at 21°C, in $CHCl_3$, lit. -10.2 (c = 0.87 g/100ml) in $CHCl_3$.[8g] (c) Enantiomeric ratio was estimated from the benzoyl ester of hydroxyl lactone **(-)-20** and subsequent analysis by HPLC using 95:5 hexane-isopropanol mobile phase, pumped at 1.5 ml/minute, using a Chiralpak-OD column, a variable wavelength detector set to 254 nm, and was determined as a ratio of relative peak area without standardization. (d) The absolute configuration was inferred from the sign of optical rotation, while the relative configuration was inferred from comparison of hydroxylactone **(-)-20** spectra with those in literature.[8g]

The results from the catalyst screen are in good agreement with the model proposed by Shi *et al*. for the stereoselectivity observed in reactions catalyzed by ketones **84b-d**.[37c] It was deduced that hydrophobic interactions between the hydrocarbon tail of the catalysts **84b-d** and aliphatic tail of the substrate govern stereoinduction as opposed to steric repulsion effects between *trans*-olefins and the *spiro*-functionality of the diketal catalyst **82** that dominate the mechanism of stereoinduction in this class.[29] The greater the length of the hydrocarbon tail of the catalyst the stronger the hydrophobic interaction with the catalyst appeared to be, leading to a greater energy bias for the **TS1** transition

state (Figure 6). It was not difficult to imagine, considering the applicability of the model of stereoinduction based on hydrophobic interactions and the apparent amphiphilic nature of both substrate and catalyst, that the formation of substrate-catalyst mixed aggregates in the biphasic system may play a role in governing the overall stereoinduction of this process. Work on probing interaction effects between classes of catalysts and fatty acid substrates (*i.e.*, non-linear effects on initial enantioselectivity with respect to catalyst concentration and mole fractions of mixtures of catalysts) would be warranted to better understand this relatively uncommon form of stereoinduction in the realm of chemical catalysis.

The **(-)-2** and **(-)-1** diastereomers of MOP were synthesized from the *R*,*R*-hydroxylactone **(-)-20** using epoxidation catalyst **84d** by the same diastereodivergent acetylation strategy employed in the earlier racemic synthesis to afford **(±)-1** and **(±)-2** (Scheme 25).



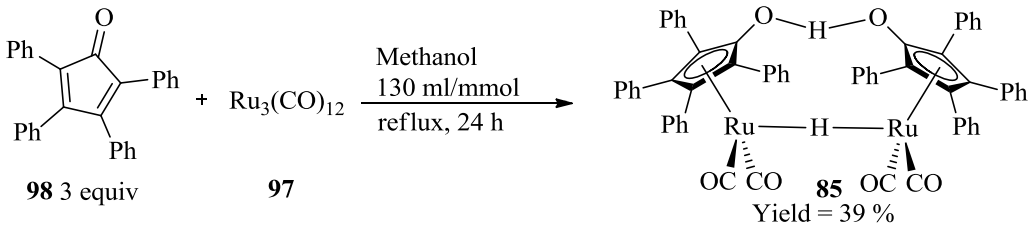
Scheme 25. Esterifications of Enantioenriched Hydroxylactone ((-)-20)

Surprisingly, the opposite diastereomer was present in each acetylated product in a ratio estimated at 1:10 with respect to the desired diastereomer. The appearance of the second

diastereomer was not attributed to a change in the relative geometry of the starting lactone, which would be mechanistically improbable given the reaction conditions. It was considered more likely that the trace diastereomeric impurity was present in the starting hydroxylactone **(-)-20**, but was not detected by ^{1}H NMR of the alcohol because the assignment was based on characteristic signals arising from one proton. In the acetylated product, the methyl protons of acetates on *threo*-**(-)-2** and *erythro*-**(-)-1** products were resolved and produced a much stronger signal arising from three protons on the methyl group, thereby allowing for the detection of the trace impurity. For this reason, it can be assumed that the enantiomeric ratio determined from the benzoate derivative **95**, which also contained ~10 % of the corresponding diastereomer by relative peak area, was representative of the optical purity of the **(-)-1** MOP product. Due to the near identical ratio of diastereomers in both the product of direct acetylation and mesylate substitution indicate that the substitution reaction proceeded, as expected, *via* an S_N2 mechanism, consistent with observations made with racemic acetylations.

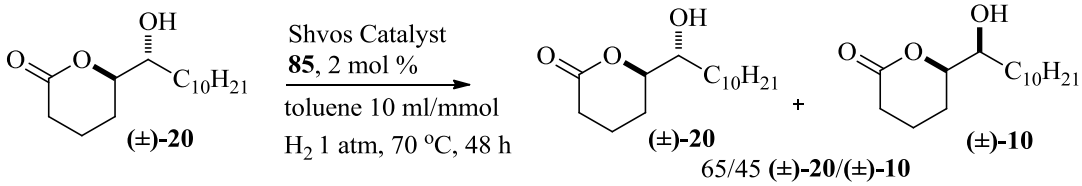
2.3 Catalytic Acylation Experiments using Dynamic Kinetic Transformation

Shvo's catalyst **85** was synthesized by heating triruthenium dodecacarbonyl **97** and tetraphenylcyclopentadienone **98** in anhydrous methanol under reflux for 24 h.[49] The air-stable dimer was obtained by filtration as a yellow powder in 39 % yield (Scheme 26).[49]



Scheme 26. Synthesis of Shvo's Catalyst

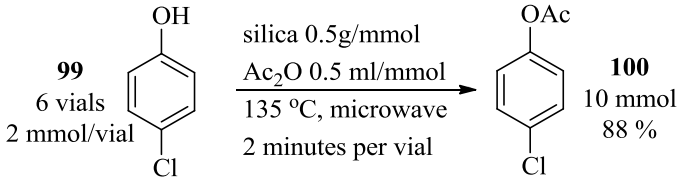
Although the synthesis of the catalyst was low yielding, the expedience and single-step synthesis made this route ideal for maintaining a supply of catalyst for screening reaction conditions and initial epimerization studies. With the catalyst in hand, the epimerization of *threo*-hydroxylactone **(±)-20** was probed to determine if the substrate would epimerize and to determine the steady state ratio of diastereomers formed in the presence of the ruthenium catalyst **85** (Scheme 27).



Scheme 27. Epimerization of *threo*-Hydroxylactone ((±)-20) using Shvo's Catalyst

Under the reported conditions the hydroxylactone was successfully epimerized to yield a mixture of diastereomers, as confirmed by comparison with an authentic sample of *erythro*-hydroxylactone **(±)-10** produced using the proline catalyzed aldol/Bayer-Villiger route.[10] The ratio of diastereomers was estimated using the relative integrals of C(6) protons by ^{1}H NMR. Once the successful epimerization using Shvo's catalyst **85** was established, the synthesis of the PCPA acyl donor **100** was required to probe the one pot dynamic kinetic transformation (DKT) conditions. This was accomplished using a

modified solvent-free acetylation of *p*-chlorophenol (**99**) under microwave conditions (Scheme 28).[50]



Scheme 28. Synthesis of *p*-Chlorophenyl Acetate under Microwave Conditions

To adequately scale up the original procedure (1 mmol scale), a screen of reaction scales and concentrations was conducted (Table 9).

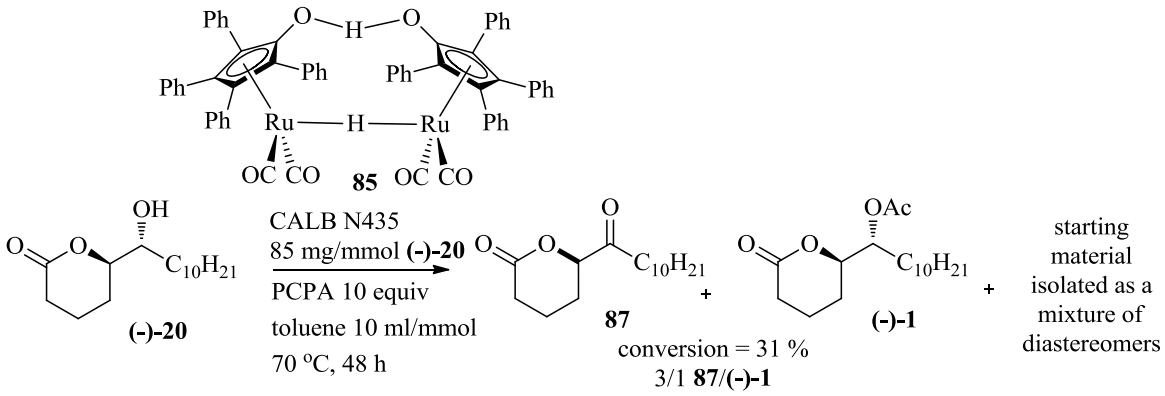
Table 9. Scaling of Microwave Synthesis of PCPA

Entry	Phenol (99) (mmol)	Ac_2O (ml)	Silica (g)	Yield (%)
1[(a)]	1.0	1.0	1.0	87
2[(a)]	2.0	1.0	1.0	91
3[(a)]	4.0	1.0	1.0	79
4[(a)]	8.0	2.0	2.0	61
5[(b)]	12	6.0	6.0	88

(a) Starting materials were combined in a 5 ml microwave vial and heated to 135 °C for 2 minutes then worked up. (b) Starting materials were combined and divided into 6 x 5 ml microwave vials and were ran as a sequence for 2 minutes at 135 °C then recombined and worked up.

The results of this screen suggested that optimal yields could be obtained when using Ac_2O (0.5 ml/mmol **99**) and silica (0.5 g/mmol **99**), at a scale of 2 mmol of chlorophenol

per microwave vial. To produce 10 mmol quantities of PCPA, starting materials were combined and divided into 6 x 5 ml microwave vials (Table 9, entry 5), which were subject to heating at 135 °C for two minutes in sequence, with ~10 minutes for cooling between runs. Once the batch was completed, the contents of the vials were combined and extracted with hexane, then dried to afford the PCPA ester **100**. With a reliable source of PCPA, the first trial DKT using an optically enriched alcohol was performed (Scheme 29).



Scheme 29. Attempted Dynamic Kinetic Transformation of Enantioenriched Hydroxylactone

The initial results were not encouraging, because conversion stopped at ~30 % and a by-product was isolated with the product, which furthermore persistently co-eluted with the product spot in all normal mobile phases available in the laboratory. The ^{1}H NMR spectra indicated that some product was present as was ascertained by the appearance of the characteristic C(5) and C(6) proton signals. However, it was less clear what the diastereomeric preference for the acetylation was, but the chemical shift of the

C(6) proton suggested that the *threo*-diastereomer was the major one. At this point the identity of the by-product was completely unknown to us, however the appearance of a characteristic signal at 4.78-4.73 ppm in the ^{1}H NMR spectrum and a new carbonyl signal at 207.8 ppm in the ^{13}C NMR spectrum suggested the formation of a ketone at C(6). The ratio of intensity between the new multiplet and the C(6) proton of **(-)-20** was 3:1, which would correspond to the ratio of **87** to **(-)-1**, if this multiplet was in fact the C(5) proton of the ketone **87**. Conditions were screened, using racemic *threo*-hydroxylactone **(±)-20**, in an attempt to increase conversion, while the reaction was repeated using vinyl acetate, which was known to favour the formation of oxidized by-product in an attempt to identify the unknown by-product from acetylation using PCPA (Table 10).

Table 10. Screening Conditions for Dynamic Kinetic Transformation

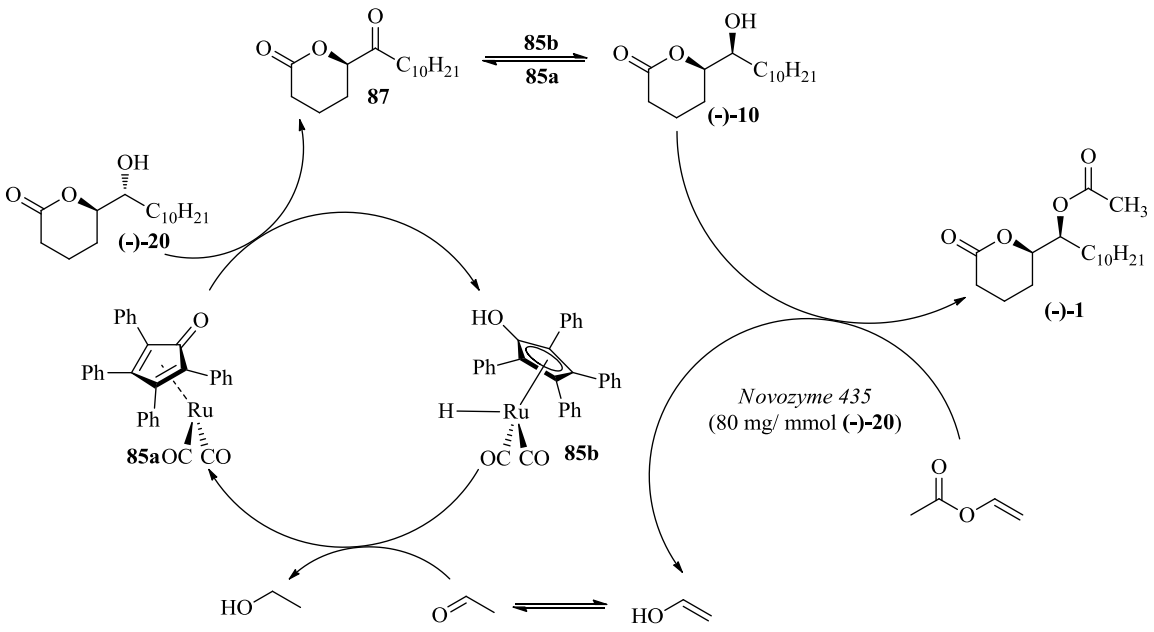
Entry	Time (days)	Atm.	Temp. (°C)	Donor	Lipase	Conv. (%)[f]	Ratio $\frac{87}{(-)\text{-}1}$[g]
1	2	N_2	70	PCPA[a]	CALB[c]	32	3
2	2	N_2	50	PCPA[a]	CALB[c]	31	3
3	2	H_2	70	PCPA[a]	CALB[c]	32	3
4	5	N_2	70	PCPA[a]	CALB[d]	32	3
5	7	N_2	70	PCPA[b]	CALA[d]	32	3
6	17[e]	N_2	70	PCPA[b]	CALB[e]	33	3
7	24	N_2	70	PCPA[b]	CALA[d]	33	3
8	2	N_2	70	VA[a]	CALB[c]	52	10

All reactions were conducted as described in the general method outlined in the experimental section. The acyl donors used were *p*-chlorophenylacetate (PCPA, **100**) and

vinyl acetate (VA). (a) Reaction was conducted using 10 equivalents of acyl donor. (b) Reaction was conducted using 15 equivalents of acyl donor. (c) Reaction was conducted using 85mg/mmol of immobilized lipase. (d) Reaction was conducted using 270 mg/mmol of immobilized lipase. (e) Reaction was initially conducted using 270 mg/mmol of immobilized lipase (86 mg), then 71 mg of lipase was added on days 9, 13, 15, 16. (f) Conversion was determined from the percentage of recovered starting material. (g) Estimated from ^{1}H NMR spectrum of the product co-eluting **87** and **(±)-1**.

It was initially thought that conversion was ceasing due to a thermal deactivation of the enzyme, however lower reaction temperature had no effect on the outcome of the reaction (Entry 2, Table 10). The reaction was repeated under a hydrogen atmosphere (1 atm) in an attempt to reduce the steady state concentration of the suspected oxidized product, with no success (Entry 3, Table 10). It was considered that the overall slowing of conversion was an effect of equilibrium control of the reaction and a series of conditions were screened to improve conversion with increased lipase loading, acyl donor equivalents and reaction time, none of which produced even a minimal effect on conversion or reduction of biproduct (Entries 4-6, Table 10). The CALB N435 immobilized enzyme was replaced with CALA enzyme immobilized on immobead150 to probe the effect of enzyme and immobilization medium, yet no effect on reaction parameters was observed (Entry 5 and 7, Table 10). Interestingly, successive additions of fresh immobilized lipase after conversion had ceased did not result in additional conversion of starting material (Entry 6, Table 10). Equilibrium considerations and the thermal or otherwise slow decay of enzyme could be ruled out as sources for the conversion limit based on these results. Instead, it was concluded that a species formed

during the course of the reaction was responsible for the inactivation of lipase once a threshold concentration was reached. Attempted DKT using vinyl acetate as a donor resulted in increased consumption of starting material, however the isolated material consisted almost exclusively of by-product (Entry 8, Table 10). Comparison of ^{1}H NMR, ^{13}C NMR spectra of the product isolate showed a very strong correlation with that isolated from previous attempts using PCPA as a donor. The mechanism for the activation of the oxidation pathway by the hydrolytic products with a vinyl acetate donor is established (Scheme 30).[40]



Scheme 30. The Oxidation of Starting Material Due to Acetaldehyde

When the spectral correlation between the two by-products is considered together with the characteristic signals suggesting the formation of a ketone at C(6), a convincing argument can be made for the tentative structural assignment of the by-product as **87**. Regardless of the structure of the by-product, it is clear from ^{13}C NMR spectra that the

by-product contained a highly deshielded carbon (208 ppm) that could compete with electrophilic acyl donor (169 ppm) for the nucleophilic serine in the active site of the lipase. The competitive reversible inhibition of lipases by methyl-*n*-alkyl ketones and aldehydes has been known for some time.[51] Although inhibition of the lipase under reaction conditions appeared to be irreversible due to the complete halt of conversion at ~30 %, the suspected oxidized by-product **87** cannot be ruled out as the source of inhibition, as its lactone moiety provides a convenient hydrogen-bond acceptor handle that could lead to greater binding affinity for the active site and therefore lead to irreversible inhibition.

3.0 Conclusions and Outlook

3.1 Racemic Synthesis[17]

The diastereoselective synthesis of the biologically active *erythro*-6-acetoxy-5-hexadecanolide was achieved in 33 % overall yield using a benign chemoenzymatic domino epoxidation-lactonization procedure. The E-factor for this oxidation/cyclization process was ~0.4, while the E-factor for the overall synthesis starting from 5-bromovaleric acid and undecanal was ~9, whereas E-factors in pharmaceutical production range between 25 and 100.[48a, b] A technique used in industrial purification of plant oils was demonstrated as a practical means of purifying a fatty acid from Wittig reactions on a gram scale. The *threo*-diastereomer was synthesized in 44 % overall yield.

At this stage the reliance on conventional means for the synthesis of fatty acid **72**, and acetylation to afford **(±)-1** has, as illustrated by E-factors provided in the experimental, introduced the largest volume of waste, and required the use of non-benign solvents. The benign oxidation procedure utilized in this work has nevertheless significantly improved upon the 'greeness' of the synthesis from previous attempts that also relied on such non-benign solvents as DCM and toluene.

Ongoing work is focused on reducing the environmental impact of the process by addressing the limitations associated with the Wittig olefination and epimerization/acetylation steps. In keeping within the tenets of green chemistry,[52] catalytic approaches to acetylation and epimerization of C(6) are being considered. To obtain the desired relative geometry, aqueous hydrolysis of the mesylate followed by lipase catalyzed acetylation is being explored as an alternative to the conventional approach taken in this work. At the same time, methods for obtaining *cis*-5-hexadecenoic acid from plant or microbial sources are being explored. The overall long term aims of this research effort are to further improve the synthesis of MOP with reduced overall waste output to render its use in mosquito control applications more feasible.

3.2 Asymmetric Synthesis

It was demonstrated that an asymmetric epoxidation of the fatty acid **72** was an efficient means to synthesize enantioenriched MOP **(-)-1** or the diastereomer **(-)-2**. High enantioselectivity (10:1 dr) for the **(-)-20** was observed for the epoxidation with the chiral ketone **84d**. Reactions using the shorter chain alkyl substituted ketones **84b**, **c** produced less optically active material in order of decreasing chain length.

The lengthy and technically challenging synthesis of the catalyst **84d** detracts from the practicality of this synthesis. Nonetheless, it provides evidence that enantioenriched alkyl lactones of the form **(-)-20** and **(-)-10** can be synthesized from unsaturated fatty acids using epoxidation and the amphiphilic nature of the substrate can be exploited for stereoinduction. The correlation between the formation of mixed aggregates in the epoxidation system and enantioselectivity should be investigated. Catalysts based on this concept could prove to become a powerful tool in asymmetric catalysis in the future.

The attempted DKT by lipase mediated acetylation of lactone **20** was unsuccessful. Reaction conversion would halt at ~7.5 %, with most of the isolated product material consisting of what is thought to be the ketone derivative **87**. This by-product was almost the exclusive product isolated from DKT using vinyl acetate as an acyl donor. The unusually downfield carbonyl carbon signal of the ketone suggested that the C(6) carbon was the more electrophilic carbonyl center among those reagents present in the reaction. It was suspected that this ketone was responsible for the inhibition of lipase.

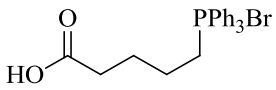
4.0 Experimental

4.1 General Procedures

Reagents and solvents were purchased at the highest available purity from Sigma-Aldrich and subsequently used from the shelf without further purification, unless otherwise stated. For use in PCPA synthesis *p*-chlorophenol was purified by vacuum distillation. Dry solvents were obtained by distillation under N_2 from CaH (DCM) or Na (toluene and THF). Procedure for the preparation of sodium *tert*-amyl oxide solution can be found in Appendix A1.2. Reactions were monitored by thin layer chromatography (TLC) using TLC silica gel plates 60 F254, EMD Merck. Flash column chromatography was performed over Silicycle ultrapure silica gel (230-400 mesh). NMR spectra were obtained with a Bruker DPX-300 (^{1}H 300 MHz or ^{1}H 600 MHz, ^{13}C 75.5 MHz, ^{15}N 60.8 MHz, ^{19}F 292 MHz) in $CDCl_3$. The chemical shifts are reported as δ values (ppm) relative to tetramethylsilane for ^{1}H NMR, ^{13}C NMR. Enantiomeric excess was measured on an Agilent 1100 series high pressure liquid chromatography (HPLC) with equipped with an OD-H column. Mass spectra were obtained on an MSI/Kratos concept IS Mass spectrometer. Optical rotations were recorded on a Perkin Elmer 341 with sodium lamp polarimeter. FT-IR spectra were obtained on an ATI Mattson Research Series spectrometer. Melting points were uncorrected. Elemental analysis was performed by combustion and gravimetric determination at Atlantic Microlab.

4.2 Detailed Experimental Procedures

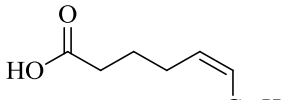
The procedures outlined in this section were previously published in reference 17.



89

(4-Carboxybutyl)triphenylphosphonium bromide (89):

A solution of triphenylphosphine (16.3 g, 62.3 mmol), and 5-bromovaleric acid (10.2 g, 56.1 mmol) in dry toluene (85 ml) was heated under reflux for 24 h. Toluene was removed *in vacuo* at 70 °C. Ether (20 ml) was added to the resulting amorphous solid and shaken vigorously. The white precipitate was filtered, washed with ether (3 x 15 ml) and dried *in vacuo* for 4 h at 35 °C to yield the title compound as a white solid that was used in subsequent reactions without further purification (21.6 g, 86 %, E = 0.2). m.p.: 191-193 °C (toluene-ether); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.5 (s, 1H), 7.82 (m, 15H), 3.64 (m, 2H), 2.30 (t, J = 7.2 Hz, 2H), 1.68 (m, 4H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 174.5, 135.38, 135.35, 134.1, 134.0, 130.8, 130.6, 118.6, 118.4, 33.06, 25.8, 25.6, 21.7, 20.8, 20.14.

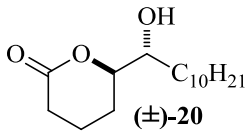


72

(*Z*)-5-Hexadecenoic acid (72):

To a flame-dried flask containing 4-(carboxybutyl)triphenylphosphonium bromide (6.01 g, 13.6 mmol), was added an 0.8 M solution of sodium *t*-amylate in *t*-amyl alcohol and 1:1 toluene:THF (38 ml), at 0 °C, under a nitrogen atmosphere and with moderate to fast

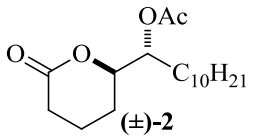
stirring with a magnetic stir bar. To the resulting viscous orange suspension was added undecanal (2.54 g, 14.9 mmol) over 10 minutes with vigorous stirring under the conditions described above. The reaction was allowed to warm to room temperature overnight. The cream coloured mixture was extracted with H_2O (4 x 10 ml). The combined aqueous phase was cooled in an ice bath and slowly brought to pH ~2 by dropwise addition of aqueous 2% H_2SO_4 solution, extracted with ether (3 x 10 ml), combined organic layers were dried ($MgSO_4$) and concentrated to a clear yellow oil (3.62 g). The crude oil was dissolved in methanol (6.6 ml) and transferred hot to a boiling solution of urea in methanol (16.5 g in 26 ml). The solution was allowed to crystallize overnight then filtered. The collected urea crystals were dissolved in 2% H_2SO_4, extracted with ether (3 x 10 ml), dried ($MgSO_4$), and ether was removed *in vacuo* to yield **7** as clear, nearly colourless oil containing about 10 % aromatic impurities by ^{1}H NMR (2.78 g). The analytically pure fatty acid was obtained by repeating the above process to yield **7** as a clear, colourless oil (2.56 g, 74 %, *Z*:*E* = 8:2, E = 3.6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.5 (s, 1H), 5.46-5.32 (m, 2H), 2.36 (t, *J* = 6.7 Hz, 2H), 2.14-2.01 (m, 4H), 1.74-1.70 (m, 2H), 1.35-1.10 (m, 18 H), 0.92-0.87 (t, *J* = 6.7 Hz, 3H) ; ^{13}C NMR (600 MHz, $CDCl_3$): δ 180.5, 131.3, 128.1, 33.4, 31.9, 29.8-29.2, 27.3, 26.5, 24.5, 22.6, 14.1; IR (KBr pellet): ν 3500-2500, 2920, 2856, 1710, 1460, 1410, 935 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{30}O_2$ $[M + H]^+$, 255.2324;found, 255.2304. Characterization data were in good agreement with literature.[12c]



(±)-20

***threo*-6-Hydroxy-5-hexadecanolide ((±)-20):**

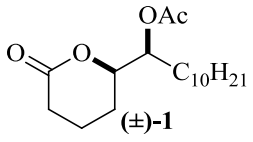
A solution of fatty acid **72** (376 mg, 1.48 mmol) in cyclohexane (7 ml) was added in aliquots (2 ml) to a vial containing CALB on Immobead 150^{TM} (126 mg) with gentle stirring over 24 h. At the same time, to the above mixture was added 15 M aqueous H_2O_2 at a rate of 0.04 ml/h *via* syringe pump and PTFE tubing (0.8 ml). Reaction mixture was stirred for an additional 24 h upon addition of all reagents, then filtered; phases were separated, the combined organic layer was dried ($MgSO_4$), adjusted to 27 ml with cyclohexane with 0.04 % (v/v) Et_3N then heated under reflux for 12 h. The resulting solution was concentrated and **(±)-20** was crystallized from hot hexane as a white solid containing only the *threo*-diastereomer **(±)-20** (196 mg, 48 %). The mother liquor was concentrated and purified by flash chromatography (1:1 hexane/EtOAc 0.02 % Et_3N) to yield **(±)-20** as a white solid (79 mg, 21 %). The two were combined to yield **(±)-20** as a white powder (275 mg, 69 %, E = 0.4) mp: 65-67 ^{o}C (hexanes), lit.[8g] 68-70 ^{o}C (hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.2 (m, 1H), 3.6 (m, 1 H), 2.6-2.5 (m, 2H), 2.0-1.2 (m, 22H), 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.6, 83.2, 73.3, 32.6, 31.9, 29.5, 25.4, 24.2, 22.7, 18.4, 14.1; IR (KBr pellet): ν 3554(br), 2955, 1706 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{30}O_3$ $[M + H]^+$ 271.2273, found 271.2258; Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.77; H, 11.15. Characterization data were in good agreement with literature.[8g]



(±)-2

***threo*-6-Acetoxy-5-hexadecanolide ((±)-2):**

To a solution of lactone **(±)-20** (342 mg, 1.27 mmol) in CH_2Cl_2 (7.6 ml) was added Ac_2O (0.72 ml, 7.56 mmol) and pyridine (0.61 ml, 7.56 mmol) at 0 ^oC under nitrogen. The reaction was allowed to slowly warm to room temperature. Upon stirring for 40 h the reaction was quenched by addition of brine (18 ml) and stirred vigorously for an additional 30 minutes. The mixture was extracted with CH_2Cl_2 (3 x 10 ml), the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (1:1 hexane-EtOAc 0.01 % Et_3N) to yield **(±)-2** as a clear colourless oil (392 mg, 98 %, E = 0.3). ^1H NMR (300 MHz, $CDCl_3$): δ 5.00 (m, 1H), 4.37 (dt, *J* = 4.5, 3.6, 1 H), 2.60-2.47 (m, 2H), 2.11 (s, 3H), 2.01-1.50 (m, 6H), 1.27 (s, 16H) 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.9, 170.7, 79.8, 73.9, 31.9, 29.9-29.3, 25.3, 24.1, 22.7, 21.0, 18.4, 14.1; HRMS (EI): m/z calcd for $C_{18}H_{32}O_4$ $[M]^+$ 312.2301, found 312.2313. Characterization data were in good agreement with literature.[8g]



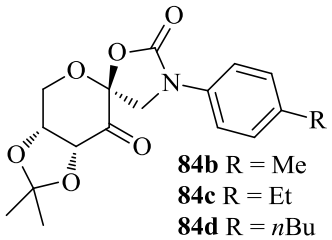
(±)-1

***erythro*-6-Acetoxy-5-hexadecanolide ((±)-1):**

A flame-dried two neck flask equipped with a magnetic stir bar, rubber septum and a vacuum adapter connected to a two-line Schlenk manifold was charged with a solution of *threo*-hydroxylactone **(±)-20** (164.7 mg, 0.609 mmol) in CH_2Cl_2 (15 ml) under N_2. The above solution was cooled in an ice bath then MsCl (0.05 ml, 0.646 mmol) and Et_3N (0.05 ml, 0.358 mmol) were added dropwise at 0 ^oC under N_2. The reaction flask was allowed to warm to room temperature over 0.5 h, then the reaction mixture was washed with water (10 ml), sat. $NaHCO_3$ (10 ml) and brine (10 ml), then dried ($MgSO_4$) and concentrated. The crude mesylate was further dried under vacuum (0.1 mmHg, 40 ^oC, 2 h), then dissolved in dry toluene (15 ml) under N_2. To a flame-dried two neck flask equipped with a magnetic stir bar, septum and condenser attached to a two-line Schlenk manifold was added CsOAc (311.8 mg, 1.628 mmol) and 18-crown-6 (180.3 mg, 0.682 mmol) under a rapid flow of nitrogen. The contents of the reaction flask were further dried by vacuum purging and backfilling with N_2 three times at 100 ^oC. The mesylate solution was transferred to the reaction flask *via* cannula with rapid stirring under N_2. The reaction mixture was heated under reflux for 16 h. The mixture was then cooled to room temperature, poured into Et_2O (30 ml) and washed with water (10 ml), sat. $NaHCO_3$ (10 ml) and brine (10 ml), then dried ($MgSO_4$), concentrated and purified by flash chromatography (2:1 hexane-EtOAc 0.02 % Et_3N) to afford **(±)-1** as a clear colourless oil (139.8 mg, 73 %, E = 4.5). ^1H NMR (300 MHz, $CDCl_3$): δ 4.95 (m, 1H), 4.32 (m, 1 H), 2.56-2.39 (m, 2H), 2.04 (s, 3H), 2.01-1.70 (m, 3H), 1.62 (m, 3H) 1.22 (s, 16H) 0.84 (t, *J*

= 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.8, 170.4, 80.5, 74.2, 31.8, 29.6-29.3, 25.2, 23.4, 22.6, 21.0, 18.3, 14.1; HRMS (EI): m/z calcd for $C_{18}H_{32}O_4$ [M]$^+$ 312.2301, found 312.2303. Characterization data were in good agreement with literature.[8g]

Catalysts **84b**-**d** were synthesized according to previously outlined representative synthetic procedures.[37a, b] Shi epoxidation conditions were based on published representative epoxidation procedures.[37c] Characterization data for catalysts were in good agreement with literature.[37a]



84b R = Me
84c R = Et
84d R = *n*Bu

Catalyst (84b):

White granular crystals; m.p. 162-163 °C (hexanes-EtOAc), lit.[37a] 162.0-163.5 °C (hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.89 (d, *J* = 5.4 Hz, 1H), 4.78-4.75 (d, *J* = 10.5 Hz, 1H), 4.67-4.64 (m, 2H), 4.31-4.26 (d, *J* = 14.1 Hz, 1H), 3.78-3.75 (d, *J* = 10.2 Hz, 2H), 2.36 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 195.1, 151.2, 134.8, 134.5, 129.8, 118.8, 111.1, 99.1, 77.5, 75.5, 60.9, 49.8, 27.1, 26.0, 20.8.

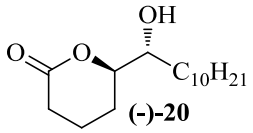
Catalyst (84c):

Clear plate-like crystals; m.p. 135-136 °C (hexanes-EtOAc), lit.[37a] 135-136 °C (hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.3 Hz, 2H), 7.23 (d, *J* = 9.3 Hz, 2H), 4.89 (d, *J* = 5.4 Hz, 1H), 4.78-4.74 (d, *J* = 10.5 Hz, 1H), 4.67-4.64 (m, 2H), 4.31-

4.26 (d, *J* = 13.8 Hz, 1H), 3.78-3.75 (d, *J* = 10.5 Hz, 2H), 2.65 (m, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.23 (t, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 195.1, 151.2, 141.2, 134.6, 128.6, 118.9, 111.1, 99.1, 75.5, 60.9, 49.8, 28.2, 27.1, 26.0, 15.6.

Catalyst (84d):

Clear plate-like crystals. m.p. 165-166 °C (hexanes-EtOAc), lit.[37a] 164-166 °C (hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 4.89 (d, *J* = 5.4 Hz, 1H), 4.78-4.74 (d, *J* = 10.5 Hz, 1H), 4.67-4.62 (m, 2H), 4.30-4.26 (d, *J* = 13.2 Hz, 1H), 3.78-3.75 (d, *J* = 10.5 Hz, 2H), 2.61 (m, 2H), 1.59 (m, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.33 (m, 2H), 0.93 (t, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 195.1, 151.2, 139.9, 134.6, 129.2, 118.8, 111.1, 99.1, 75.5, 60.9, 49.8, 34.9, 33.6, 27.1, 26.0, 22.24, 13.9.



(-)-20

(5R, 6R)-6-hydroxy-5-hexadecanolide ((-)-20) by Representative Shi Epoxidation:

To a solution of fatty acid **72** (200 mg, 0.786 mmol) and catalyst **84d** (76 mg, 0.196 mmol) in DME-DMM 3:1 (12 ml) was added an aqueous buffer (7.9 ml, 0.1 M AcOH-K_2CO_3 pH 9.3 in 0.4 mM aqueous EDTA) and Bu_4NHSO_4 (10 mg, 0.031 mmol) with vigorous stirring. The solution was cooled in a -11 ^{o}C ice-salt bath for 15 minutes then solutions of Oxone (6.3 ml, 0.20 M in 0.4 mM aqueous EDTA) and K_2CO_3 (6.3 ml, 0.84 M in 0.4 mM aqueous EDTA) were delivered simultaneously over 6 hours. The solution

was adjusted to pH ~2 by slow addition of 10% HCl (3.5 ml), extracted with EtOAc (3 x 10ml), dried ($MgSO_4$), filtered and concentrated. The crude oil was dissolved in cyclohexane (14 ml) and heated under reflux for 24 hours. The resulting yellow solution was concentrated and purified by flash chromatography (Et_2O) then recrystallized from hexanes to afford the target compound **(-)-20** as a white solid (149 mg, 70 %). m.p. 65-66 ^oC (hexanes), lit.[8g] 68-70 ^oC (hexanes-EtOAc); $[\alpha]_D$ -9.3^o (c = 0.95, $CHCl_3$); lit.[8g] -10.2 ^{o} (c = 0.87); ^1H NMR (300 MHz, $CDCl_3$): δ 4.2 (m, 1H), 3.6 (m, 1 H), 2.6-2.5 (m, 2H), 2.0-1.2 (m, 22H), 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.6, 83.2, 73.3, 32.6, 31.9, 29.5, 25.4, 24.2, 22.7, 18.4, 14.1; IR (KBr): ν 3554(br), 2955, 1706 cm^{-1};HRMS (FAB): m/z calcd for $C_{16}H_{30}O_3$ $[M + H]^+$ 271.2273, found 271.2262.

Hydroxylactone ((-)-20) using catalyst (84b):

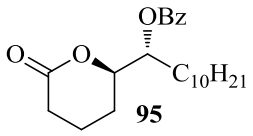
Starting with fatty acid **72** (254 mg, 1.00 mmol) the representative epoxidation procedure using catalyst **84b** was followed to synthesise **(-)-20** as a white solid (175 mg, 65 %). m.p 65-67 ^oC (hexanes), lit.[8g] 68-70 ^oC (hexanes-EtOAc); $[\alpha]_D$ -6.5^o (c = 1.04, $CHCl_3$); lit.[8g] -10.2 ^{o} (c = 0.87, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.2 (m, 1H), 3.6 (m, 1 H), 2.6-2.5 (m, 2H), 2.0-1.2 (m, 22H), 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.6, 83.2, 73.3, 32.6, 31.9, 29.5, 25.4, 24.2, 22.7, 18.4, 14.1.

Hydroxylactone ((-)-20) using catalyst (84c):

Starting with fatty acid **72** (255 mg, 1.00 mmol) the representative epoxidation procedure using catalyst **84c** was followed to synthesis **(-)-20** as a white solid (183 mg, 68 %). m.p. 65-67 ^oC (hexanes), lit.[8g] 68-70 ^oC (hexanes-EtOAc); $[\alpha]_D$ -8.6^o(c = 1.01, $CHCl_3$),

lit.[8g] -10.2 ^{o} (c = 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.2 (m, 1H), 3.6 (m, 1 H), 2.6-2.5 (m, 2H), 2.0-1.2 (m, 22H), 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.6, 83.2, 73.3, 32.6, 31.9, 29.5, 25.4, 24.2, 22.7, 18.4, 14.1.

Characterization data were in good agreement with literature for all asymmetric epoxidation products.[8g]

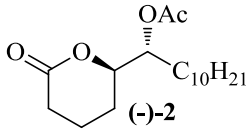


95

(5R, 6R)-6-(OBz)-5-Hexadecanolide (95) with chirality from catalyst (84d):

To a solution of lactone **(-)-20** (43 mg, 0.16 mmol) in CH_2Cl_2 (1.0 ml) was added BzCl (0.11 ml, 0.95 mmol), pyridine (0.08 ml, 0.95 mmol) and DMAP (1.4 mg, 0.012 mmol) at 0 ^{o}C under nitrogen. The reaction was allowed to slowly warm to room temperature. Upon stirring for 2.5 h the reaction was quenched by addition of brine (3 ml) and stirred vigorously for an additional 30 minutes. The mixture was extracted with CH_2Cl_2 (3 x 10 ml), the combined organic layers were dried ($MgSO_4$) and concentrated. Hexane-EtOAc (3:1, 1 ml) was added to the residue, the resulting white precipitate was removed by filtration and the filtrate was concentrated and purified by flash chromatography (3:1 hexane-EtOAc 0.01 % Et_3N) to yield **95** as a clear colourless oil (51 mg, 85 %).; $[\alpha]_D$: -10.1 (c = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (m, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 5.27 (m, 1H), 4.52 (m, 1H), 2.62-2.46 (m, 2H), 2.01-1.59 (m, 6H), 1.48-1.25 (m, 16H), 0.88 (t *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.0, 166.1, 133.3, 129.8, 128.5, 79.9, 74.4, 31.9, 30.1, 29.7, 29.5, 29.4, 29.3, 25.5, 24.3, 22.7, 18.4, 14.1; er: 10:1

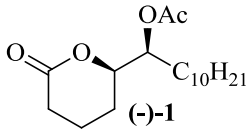
[HPLC, ChiralcelOD, hexane-isopropanol 95:5, 1.5 ml/minute, rt (area) = 11.65(584.4) and 13.90(57.2)]. Characterization data were in good agreement with literature.[53]



(-)-2

(5R, 6R)-6-Acetoxy-5-hexadecanolide ((-)-2) with chirality from catalyst (84d):

To a solution of lactone **(-)-20** (50 mg, 0.18 mmol) in CH_2Cl_2 (1.2 ml) was added Ac_2O (0.11 ml, 1.2 mmol), pyridine (0.10 ml, 1.2 mmol) and DMAP (1.4 mg, 0.012 mmol) at 0 ^oC under nitrogen. The reaction was allowed to slowly warm to room temperature. Upon stirring for 0.5 h the reaction was quenched by addition of brine (3 ml) and stirred vigorously for an additional 30 minutes. The mixture was extracted with CH_2Cl_2 (3 x 10 ml), the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (1:1 hexane-EtOAc 0.01 % Et_3N) to yield **(-)-2** as a clear colourless oil (54 mg, 97 %).; $[\alpha]_D$ -13.0° (c = 2.0, $CHCl_3$), lit.[8n] -14.4° (c = 2.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.00 (m, 1H), 4.37 (dt, *J* = 4.5, 3.6, 1 H), 2.60-2.47 (m, 2H), 2.11 (s, 3H), 2.01-1.50 (m, 6H), 1.27 (s, 16H) 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.9, 170.7, 79.8, 73.9, 31.9, 29.9-29.3, 25.3, 24.1, 22.7, 21.0, 18.4, 14.1.

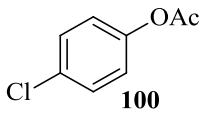


(-)-1

(5R, 6S)-6-acetoxy-5-hexadecanolide ((-)-1) with chirality from catalyst (84d):

A flame-dried two neck flask equipped with a magnetic stir bar, rubber septum and a vacuum adapter connected to a two-line Schlenk manifold was charged with a solution of

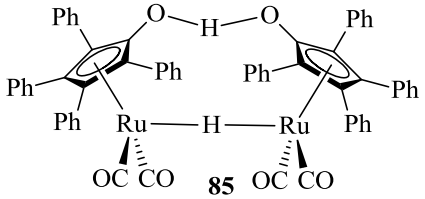
(5R, 6R)-hydroxylactone **(-)-20** (52 mg, 0.19 mmol) in CH_2Cl_2 (5 ml), under N_2. The above solution was cooled in an ice bath then MsCl (0.02 ml, 0.2 mmol) and Et_3N (0.02 ml, 0.1 mmol) were added dropwise at 0 ^oC under N_2. The reaction flask was allowed to warm to room temperature over 0.5 h, then the reaction mixture was washed with water (3 ml), sat. $NaHCO_3$ (3 ml) and brine (3 ml), then dried ($MgSO_4$) and concentrated. The crude mesylate was dried under vacuum (0.1 mmHg, 40 ^oC, 2 h), then dissolved in dry toluene (5 ml) under N_2. To a flame-dried two neck flask equipped with a magnetic stir bar, septum and condenser attached to a two-line Schlenk manifold was added CsOAc (92 mg, 0.48 mmol) and 18-crown-6 (56 mg, 0.21mmol) under a rapid flow of nitrogen. The contents of the reaction flask were further dried by vacuum purging and backfilling with N_2 three times at 100 ^oC. The mesylate solution was transferred to the reaction flask via cannula with rapid stirring under N_2. The reaction mixture was heated under reflux for 16 h. The mixture was then cooled to room temperature, poured into Et_2O (10 ml) and washed with water (3 ml), sat. $NaHCO_3$ (3 ml) and brine (3 ml), then dried ($MgSO_4$), concentrated and purified by flash chromatography (2:1 hexane-EtOAc 0.02 % Et_3N) to afford **(-)-1** as a clear colourless oil (46 mg, 77 %). $[\alpha]_D$: -34.1° (c = 2.0, $CHCl_3$), lit.[8g] -38.1° (c = 1.02 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.95 (m, 1H), 4.32 (m, 1H), 2.56-2.39 (m, 2H), 2.04 (s, 3H), 2.01-1.70 (m, 3H), 1.62 (m, 3H) 1.22 (s, 16H) 0.84 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.8, 170.4, 80.5, 74.2, 31.8, 29.6-29.3, 25.2, 23.4, 22.6, 21.0, 18.3, 14.1. Characterization data were in good agreement with literature.[8g]



100

4-Chlorophenyl acetate (100):

In a 10 ml microwave vial, was added Ac_2O (1.0 ml) and silica gel (1.0 g) and stirred until a uniform silica paste was formed. To the above mixture was added 4-chlorophenol (521 mg, 4.06 mmol) and heated at 135 ^oC for 2.5 min using microwave radiation. The mixture was extracted with hexane (3 x 4 ml), dried ($MgSO_4$), filtered and residual solvent and acetic acid was removed under reduced pressure (0.1 mmHg, 30 ^oC, 3 h) to yield the title compound as a brown liquid (548 mg, 79 %). ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, 2H), 7.05 (d, 2H), 2.30 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.1, 149.2, 131.1, 129.5, 123.0, 21.0. Characterization data were in good agreement with literature.[50]



85

Synthesis of Shvo's Catalyst (85):

To a flame dried two neck flask equipped with an oval magnetic stir bar, septum, and flame dried condenser connected to a two line Schlenk manifold was added triruthenium dodecacarbonyl (100 mg, 0.157 mmol) and tetraphenylcyclopentadienone (181 mg, 0.470 mmol) under a rapid flow of N2. The flask was charged with anhydrous methanol (17 ml) and heated under reflux for 24 h. The reaction was cooled to room temperature and the yellow precipitate was collected by vacuum filtration and washing with hexanes (3 x 1 ml). Drying under reduced pressure afforded catalyst **85** as a bright yellow powder (174

mg, 39 %). ^{1}H NMR (300 MHz, benzene-d_6): δ 13.8 (s, 1H), 7.46 (m, 8H), 7.09 (m, 8H), 6.91 (m, 12 H), 6.72 (m, 12H), -17.75 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$). Characterization data were in good agreement with literature.[41]

Epimerization of ((±)-20) to ((±)-10) using Shvo`s Catalyst (85):

A flame-dried flask was charged with **(±)-20** (48 mg, 0.179 mmol), Shvo`s catalyst **85** (2 mg, 0.002 mmol) and toluene (0.85 ml) under H_2 (1 atm) and heated at 70 °C for 24 h. The solution was isolated by filtration, concentrated and purified by flash chromatography (1:1 hexanes:EtOAc) and subsequently prepared for analysis by NMR in $CDCl_3$. See Appendix A3.18for NMR spectra.

Attempted dynamic kinetic transformation of ((±)-20) using vinyl acetate donor:

A flame dried two-neck flask, equipped with stir-bar was charged with **(±)-20** (45 mg, 0.166 mmol), **85** (2 mg, 0.002 mmol) and CALB (N435, 18 mg) and dried by evacuating and flushing with N_2 three times. A second flame dried flask was charged with vinyl acetate (0.16 ml, 1.73 mmol) and dry toluene (0.83 ml) under N_2. The solution of vinyl acetate was dried by passing dry N_2 through the solution *via* syringe needle for 1 h and then transferred via cannula to the two neck flask using a positive pressure of N_2. The reaction mixture was heated under N_2 for 48 h, the solution was isolated by filtration, concentrated under reduced pressure and purified by flash chromatography (2:1 then 1:1 hexane-EtOAc 0.02 % Et_3N). Starting material was recovered as a mixture of diastereomers (21.6 mg, 48 %). The product suspected to be **87** was isolated with trace (~10 %) acetylated starting materials as clear oil. (28.0 mg) ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (m, 1H), 2.67-2.57 (m, 3H), 2.18-2.10 (m, 4H), 1.59 (m, 2H), 1.25 (s, 14H), 0.88

(t, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 207.8, 169.7, 83.3, 38.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 24.3, 22.9, 22.7, 19.9, 14.1.

Representative Dynamic kinetic transformation of chiral hydroxylactone ((+)-20) using PCPA (100):

A flame dried two-neck flask, equipped with stir-bar was charged with **(±)-20** (86 mg, 0.325 mmol), **85** (7 mg, 0.006 mmol) and CALB (N435, 94 mg) and dried by evacuating and flushing with N_2 three times. A second flame dried flask was charged with **100** (547 mg, 3.21 mmol) and dry toluene (2.0 ml) under N_2. The solution of vinyl acetate was dried by passing dry N_2 through the solution *via* syringe needle for 1 h and then transferred via cannula to the two neck flask using a positive pressure of N_2. The reaction mixture was heated under N_2 for 48 h, the solution was isolated by filtration, concentrated under reduced pressure and purified by flash chromatography (2:1 then 1:1 hexane-EtOAc 0.02 % Et_3N). Starting material was recovered as a mixture of diastereomers (59, 69 %). The product suspected to be **87** was isolated with trace (~25 %) acetylated starting materials as clear oil. (28.0 mg, see Appendix A3.20 and A3.21 for NMR spectra)

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Appendix:

A1 Supporting Experimental Procedures

A1.1 Synthesis of (*Z*)-5-hexadecenoic acid (7) using *t*-BuOK base (Table 3, entry 1 in text):

Phosphonium bromide (1.12 g, 2.53 mmol) and *t*-BuOK (750 mg, 6.33 mmol) were combined in a flame dried two neck flask equipped with an oval stir bar, a rubber septum on one neck and a vacuum adaptor connected to a two-line Schlenk tube on the side arm. The flask was evacuated then filled with N_2 three times then cooled to 0 ^oC in an ice bath, and charged with freshly distilled THF (4 ml), under N_2 and with stirring. The resulting deep orange slurry was stirred for 30 minutes then freshly distilled undecanal (464 mg, 2.72 mmol) was added dropwise over 30 minutes with vigorous stirring. The resulting pale yellow suspension was slowly allowed to warm to room temperature overnight. The cream coloured suspension was then concentrated and placed under 0.1 mmHg at 40 ^oC for 3 h. To the amorphous residue was added water (10 ml) and the flask was left overnight allowing triphenylphosphine oxide to precipitate. The resulting solution was filtered and brought to pH ~2 by slow addition of 2 % H_2SO_4 then extracted with Et_2O (4 x 4 ml), dried ($MgSO_4$), filtered and concentrated to afford a yellow oil (648 mg). The crude fatty acid residue (106 mg) was purified by flash chromatography (hexane then hexane/EtOAc 1:1) to afford the title compound as a clear colourless oil (47 mg, yield = 45 %, Z:*E* = 9:1). ^1H NMR (600 MHz, $CDCl_3$): δ 11.5 (s, 1H) 5.46-5.32 (m, 2H), 2.36 (t, *J* = 6.7 Hz, 2H), 2.14-2.01 (m, 4H), 1.74-1.70 (m, 2H), 1.35-1.10 (m, 18 H) 0.92-0.87 (t,

J = 6.7 Hz, 3H) ; ^{13}C NMR (600 MHz, $CDCl_3$): δ 180.5, 131.3, 128.1, 33.4, 31.9, 29.8-29.2, 27.3, 26.5, 24.5, 22.6, 14.1; IR (KBr pellet): ν 3500-2500, 2920, 2856, 1710, 1460, 1410, 935 cm^{-1}.

The remaining crude extract (542 mg) was purified using the urea inclusion method as described in the main text to afford the title compound as a clear colourless oil (172 mg, yield = 32 %, Z:*E* = 9:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.5 (s, 1H) 5.46-5.32 (m, 2H), 2.36 (t, *J* = 6.7 Hz, 2H), 2.14-2.01 (m, 4H), 1.74-1.70 (m, 2H), 1.35-1.10 (m, 18 H) 0.92-0.87 (t, *J* = 6.7 Hz, 3H) ; ^{13}C NMR (600 MHz, $CDCl_3$): δ 180.5, 131.3, 128.1, 33.4, 31.9, 29.8-29.2, 27.3, 26.5, 24.5, 22.6, 14.1; IR (KBr pellet): ν 3500-2500, 2920, 2856, 1710, 1460, 1410, 935 cm^{-1}.

A1.2 Preparation of sodium *t*-amylate solution and determination of base:

Generation of amylate solution in toluene-THF

t-AmOH (100 ml) was heated under reflux with sodium (2.01 g) until sodium was dissolved. The resulting solution was distilled into dry toluene (100 ml) and sodium. The distillate was heated under reflux for 8 h then transferred hot *via* cannula into an oven dried glass bottle, fitted with a septum and containing dry THF (100 ml). The solution was stored under nitrogen and at -7 ^{o}C.

Determination of Base concentration

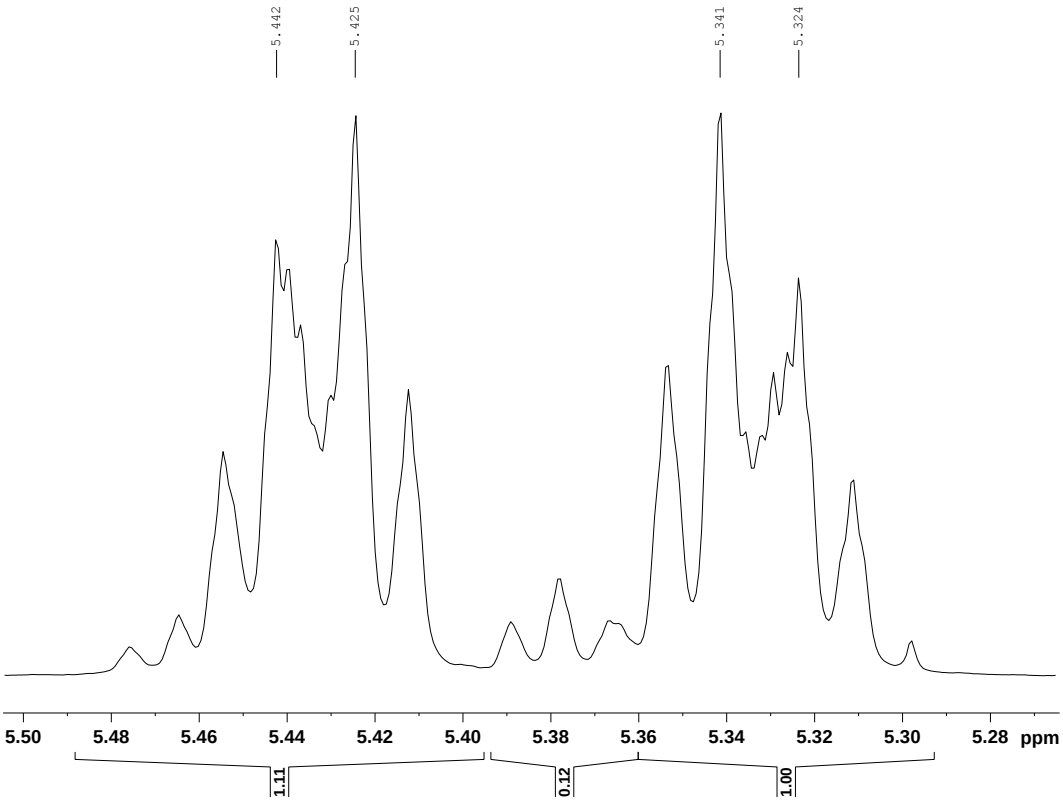
The above solution was warmed to room temperature then transferred (1.0 ml) to distilled water (10 ml) with phenolphthalein indicator. The mixture was titrated with HCl (1.0 M, 0.82 ml) until a colour change was observed.

A2.0 Determination of *Z*:*E* Ratios

Z:*E* ratio was calculated as the ratio of *E*- and *Z*- olefinic proton multiplets by ^{1}H NMR. The corresponding spectra are provided below:

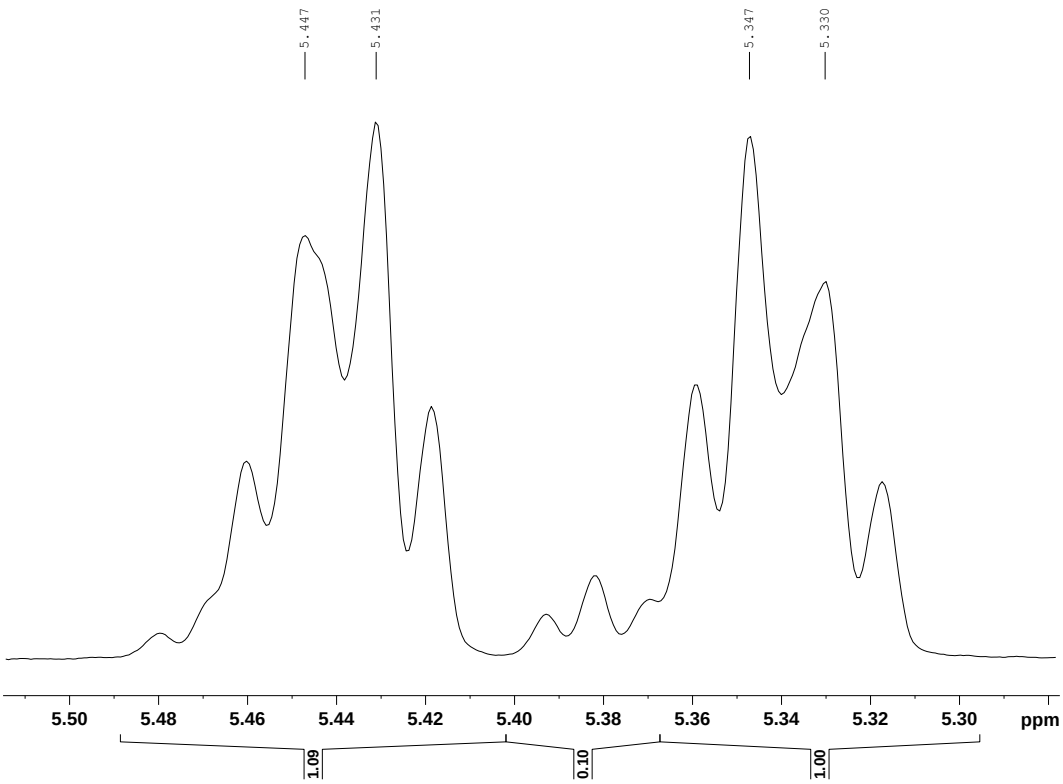
A2.1 ^{1}H NMR Multiplet analyses:

Fatty acid 72 synthesized using *t*-BuOK and isolated from column (Table 3, Entry 1 in text)



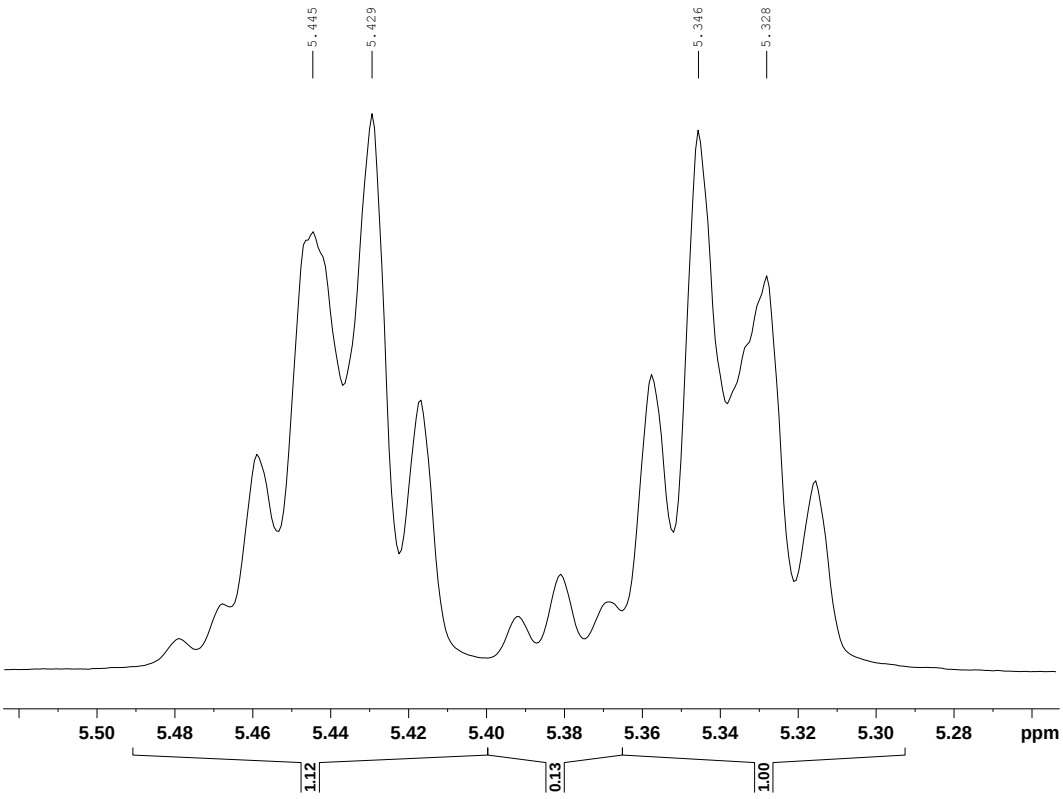
J = 10.2 Hz Major, *Z*:*E* = 8:2

Fatty acid 72 synthesized using *t*-BuOK and isolated from urea (Table 3, Entry 1 in text)



J = 9.9 Hz Major, *Z*:*E* = 8:2

Fatty acid 72 synthesized using *t*-AmONa and isolated from urea (Table 3, Entry 2 in text)

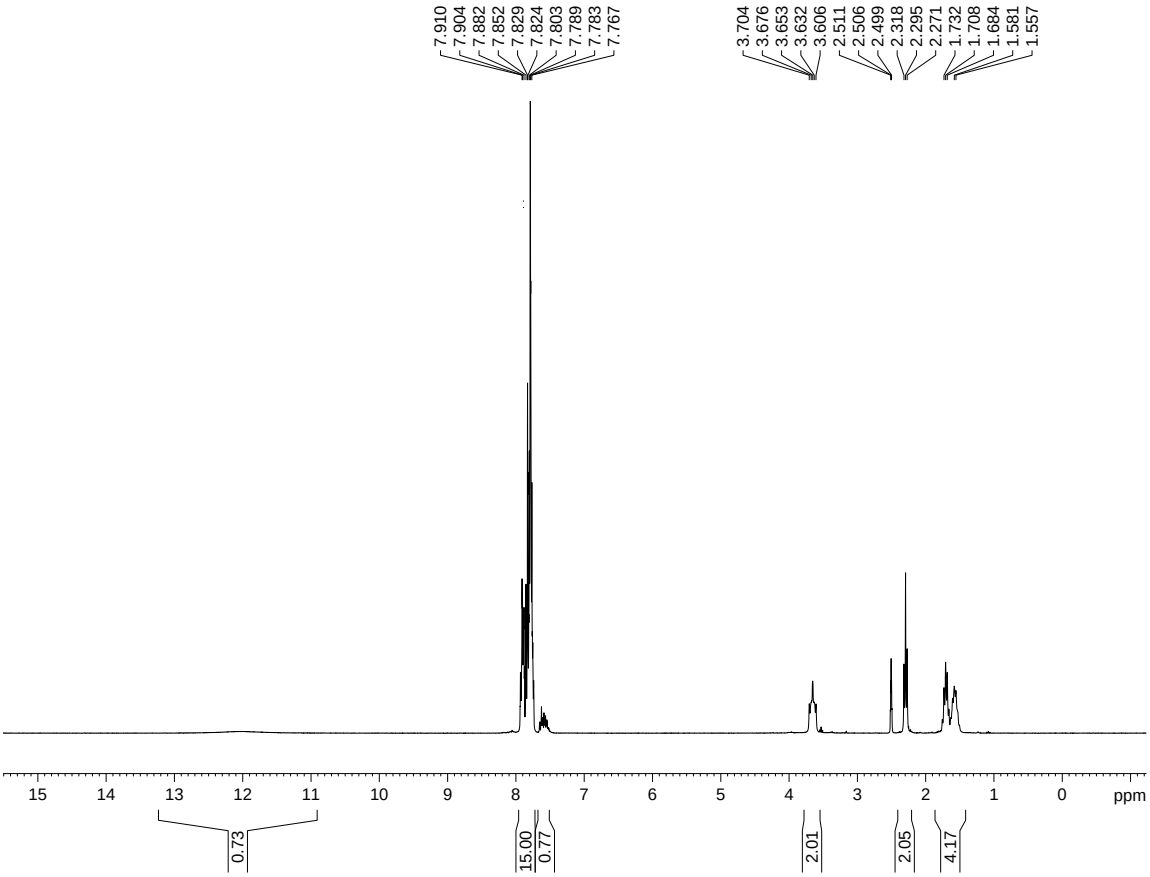


J = 10.2 Hz Major, *Z*:*E* = 8:2

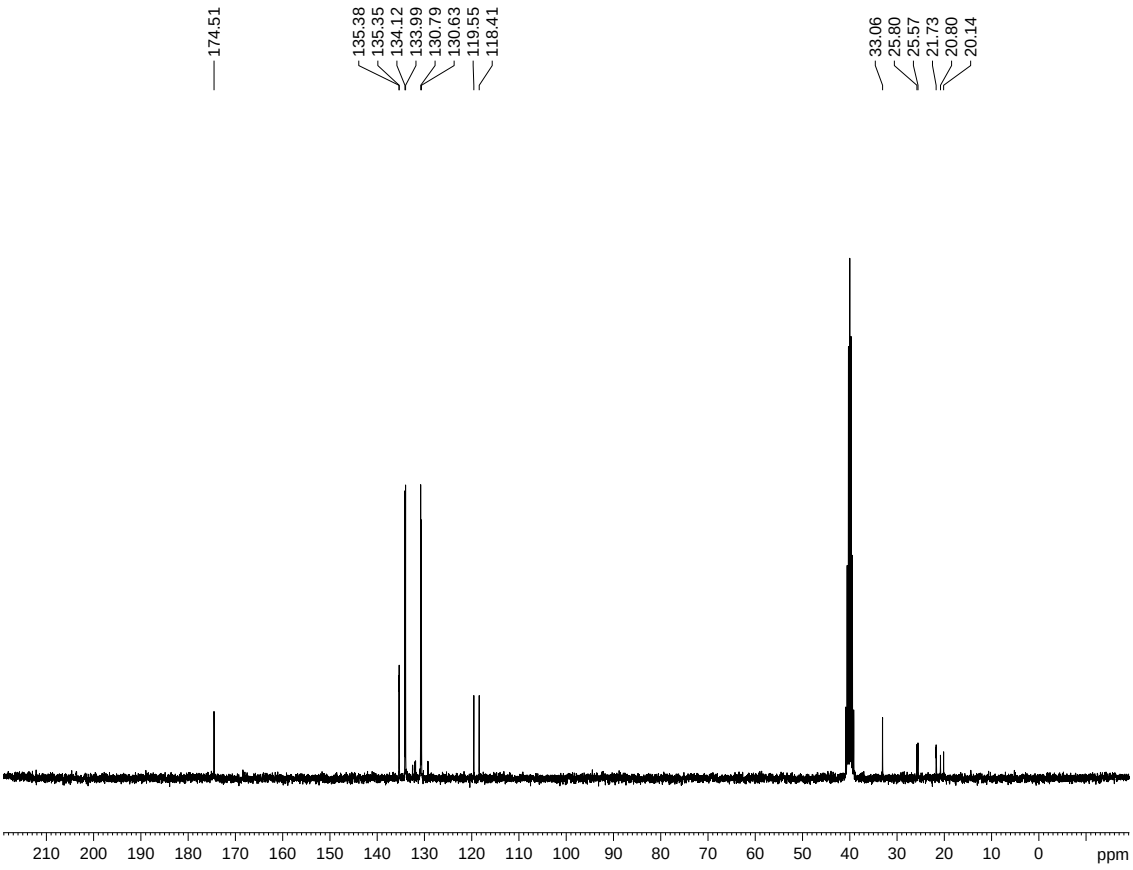
A3.0 NMR Spectra of Isolated Products and Synthetic Intermediates

A3.1 (4-carboxybutyl)triphenylphosphonium bromide (89):

^{1}H NMR, 300 MHz, DMSO-d_6

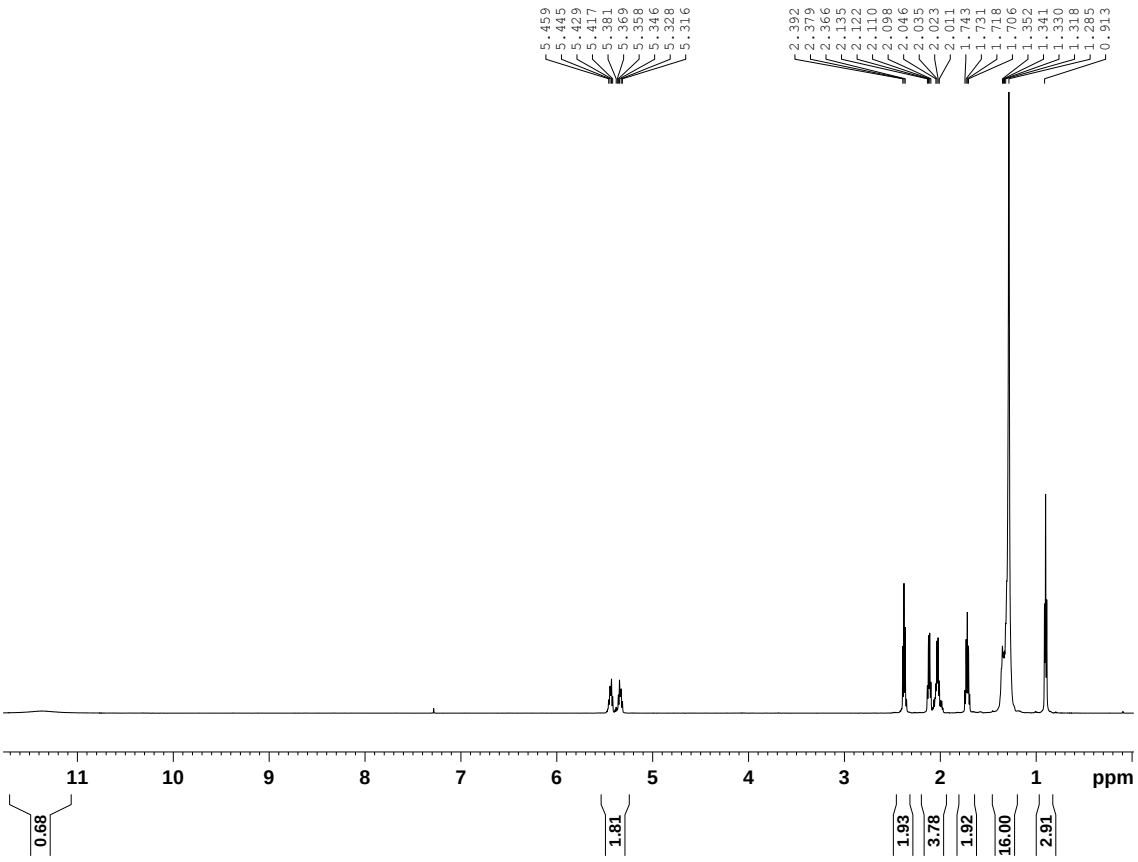


^{13}C NMR, 300 MHz, DMSO-d_6

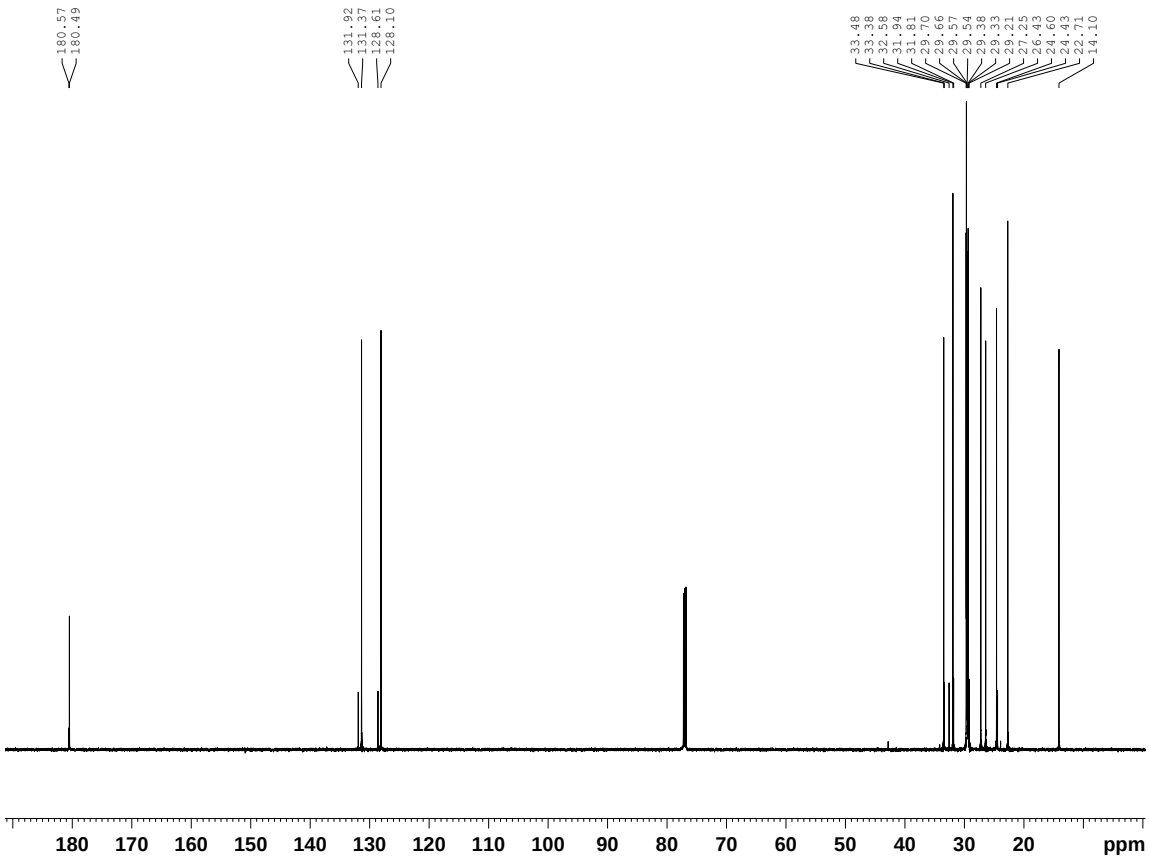


A3.2 (*Z*)-5-hexadecenoic acid (72):

^{1}H NMR, 600 MHz, $CDCl_3$

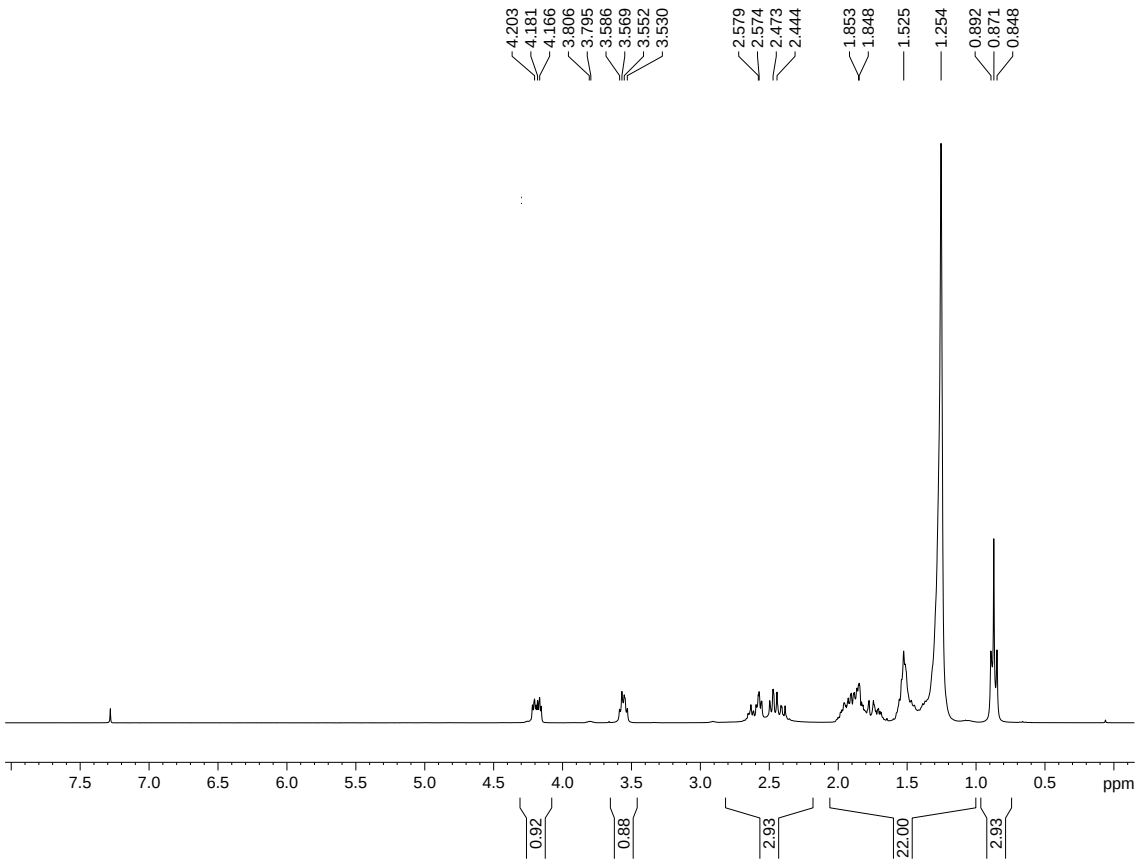


^{13}C NMR, 600 MHz, $CDCl_3$

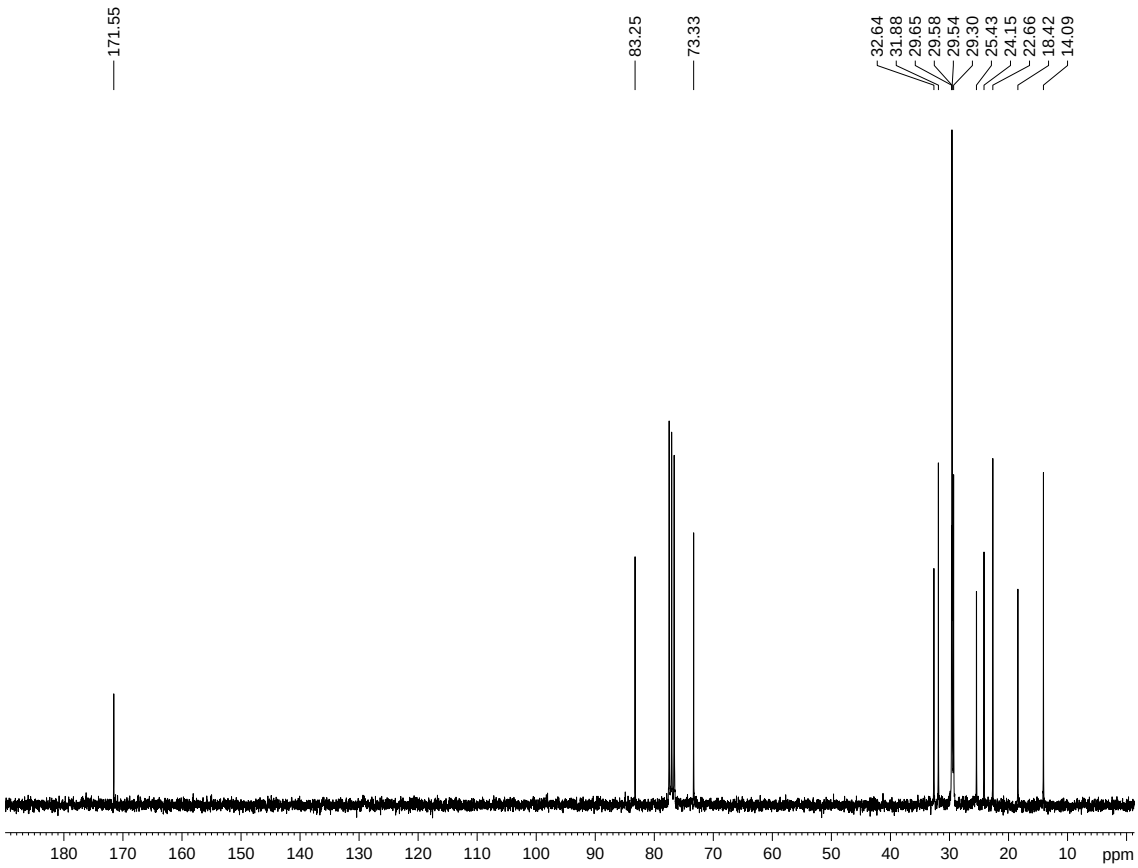


A3.3 *threo*-6-hydroxy-5-hexadecanolide ((±)-20):

^{1}H NMR, 300 MHz, $CDCl_3$

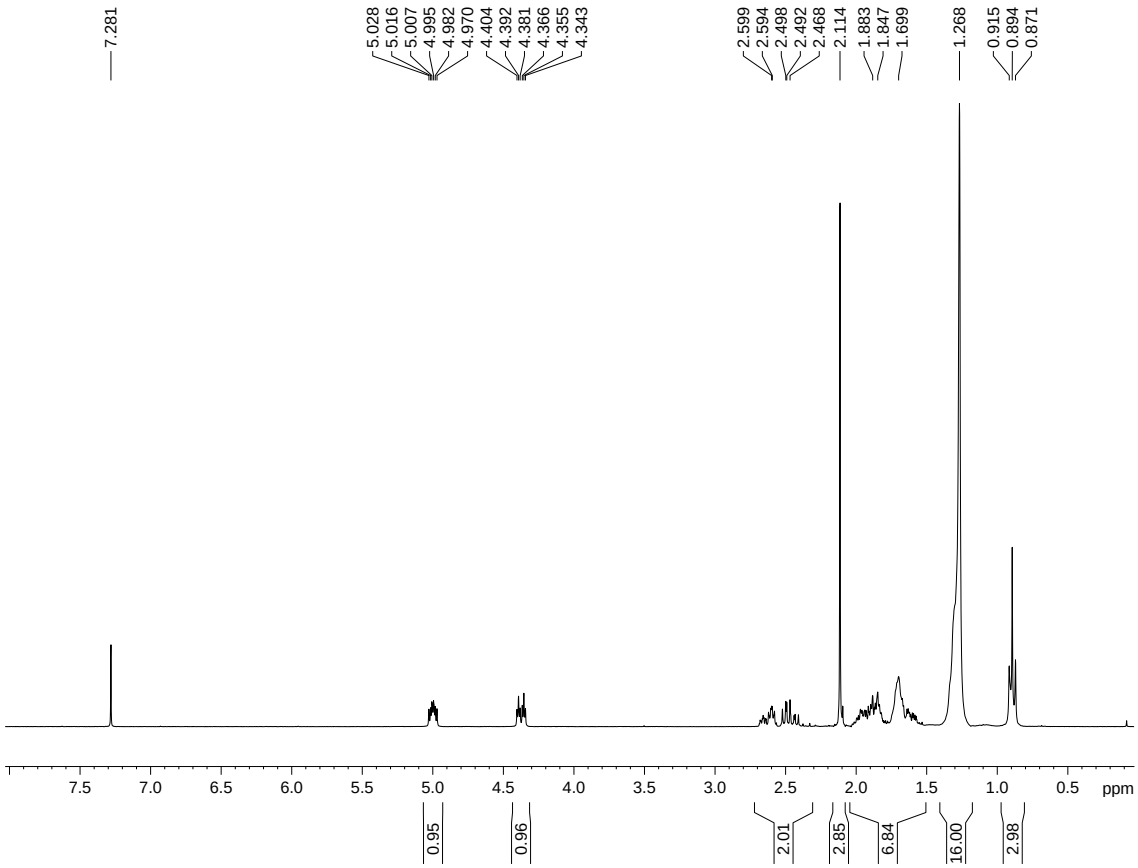


^{13}C NMR, 300 MHz, $CDCl_3$

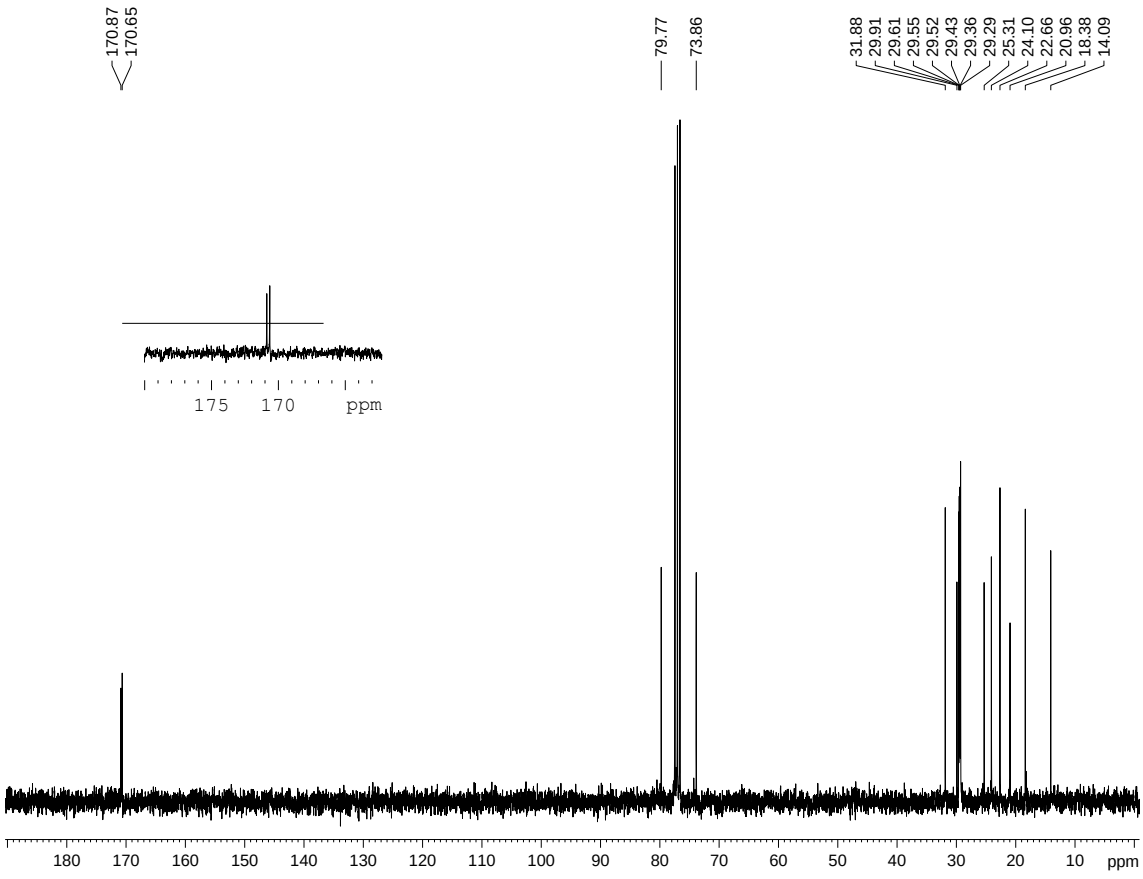


A3.4 *threo*-6-acetoxy-5-hexadecanolide ((±)-2):

^{1}H NMR, 300 MHz, $CDCl_3$

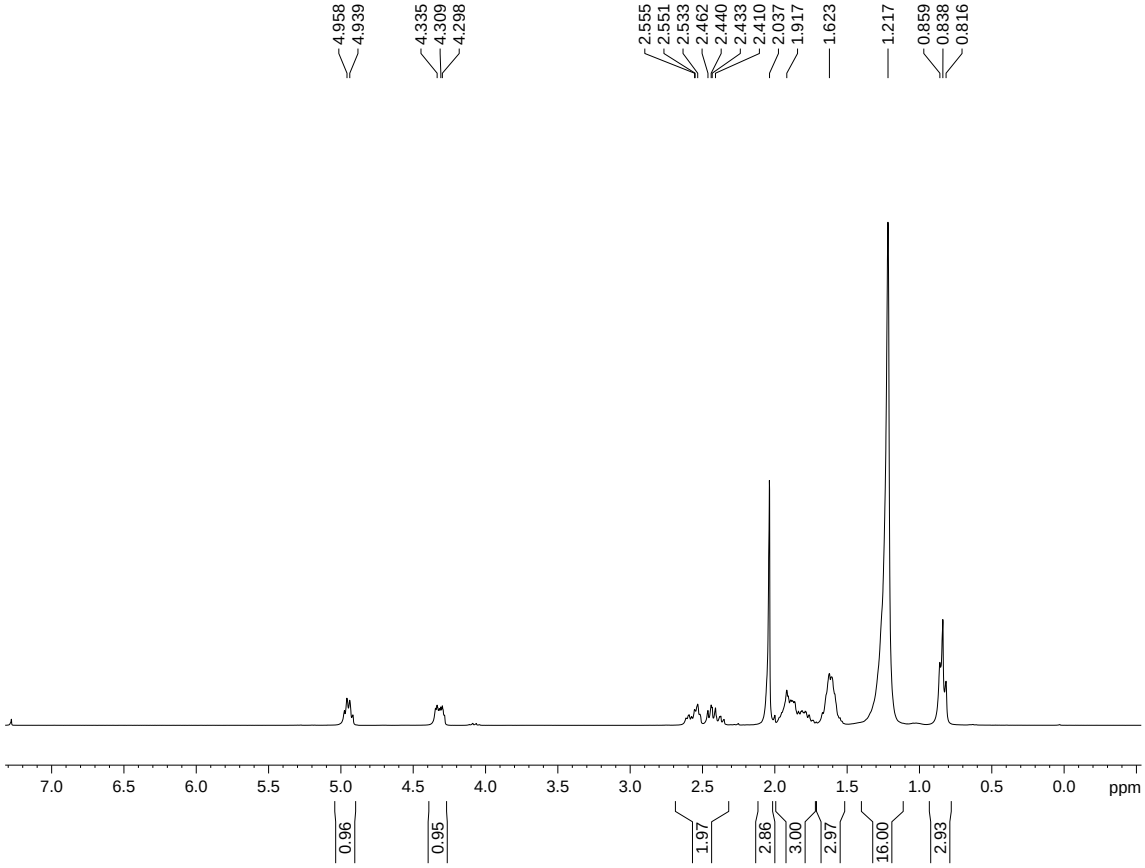


^{13}C NMR, 300 MHz, $CDCl_3$

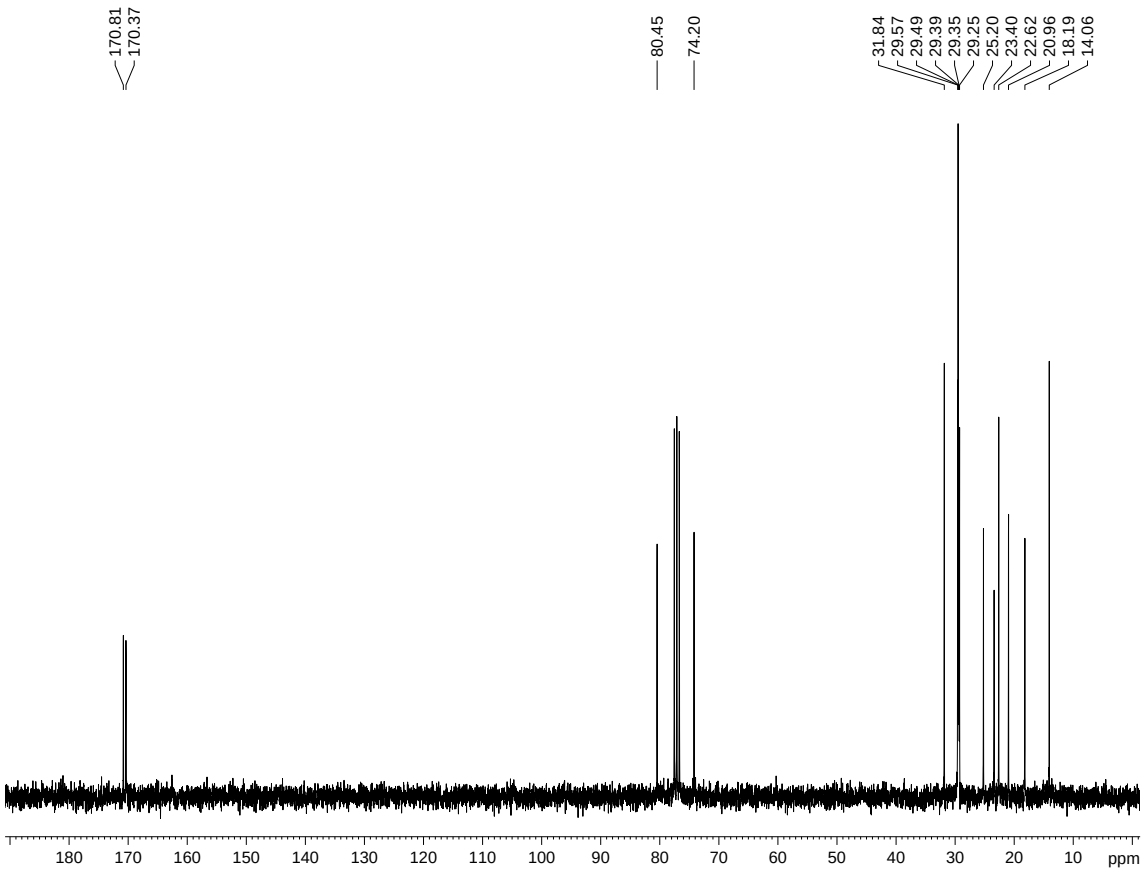


A3.5 *erythro*-6-acetoxy-5-hexadecanolide ((±)-1):

^{1}H NMR, 300 MHz, $CDCl_3$

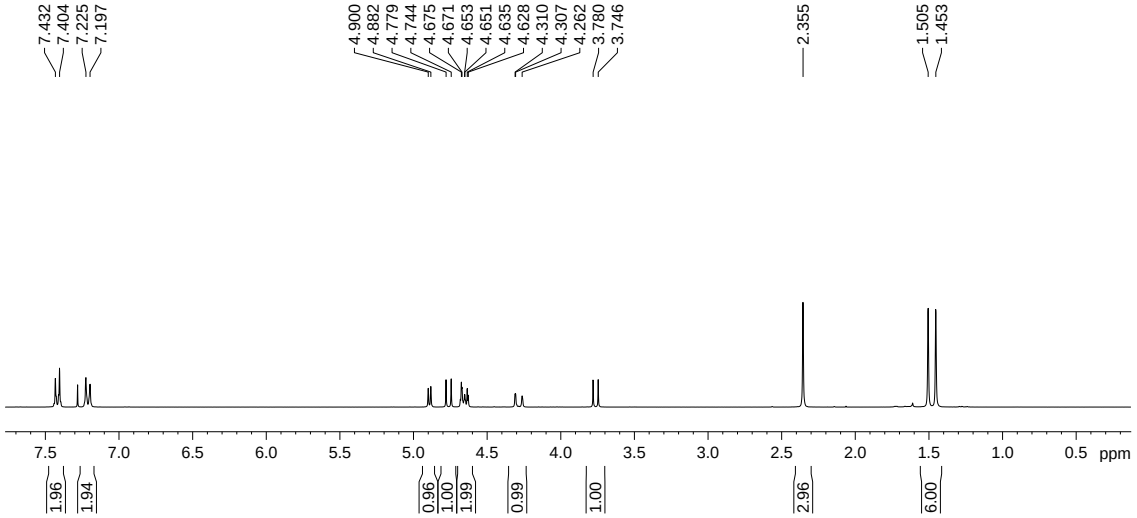


^{13}C NMR, 300 MHz, $CDCl_3$

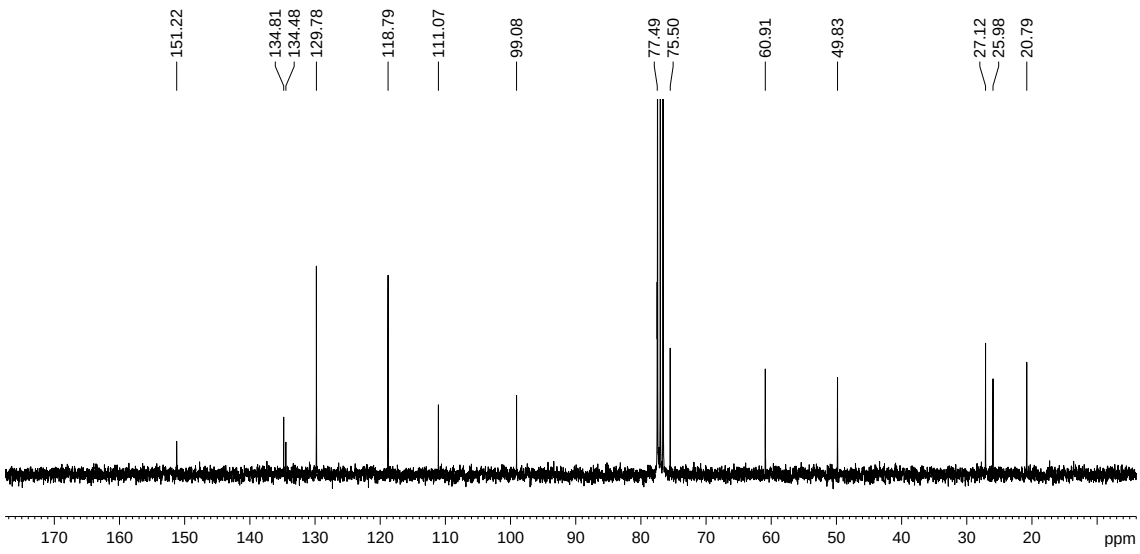


A3.6 Catalyst (84b):

^{1}H NMR, 300 MHz, $CDCl_3$

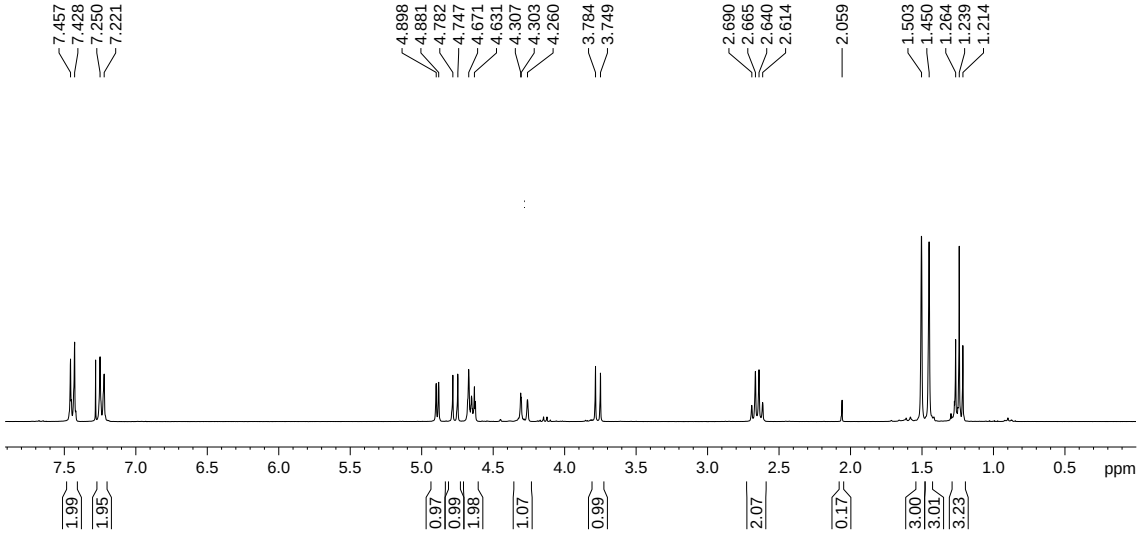


^{13}C NMR, 300 MHz, $CDCl_3$

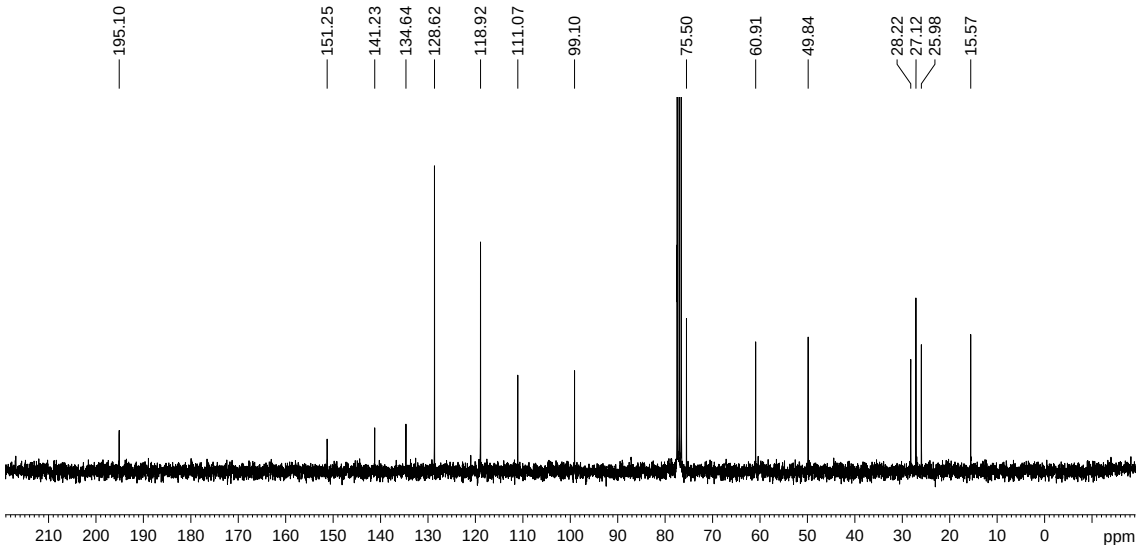


A3.7 Catalyst (84c):

^{1}H NMR, 300 MHz, $CDCl_3$

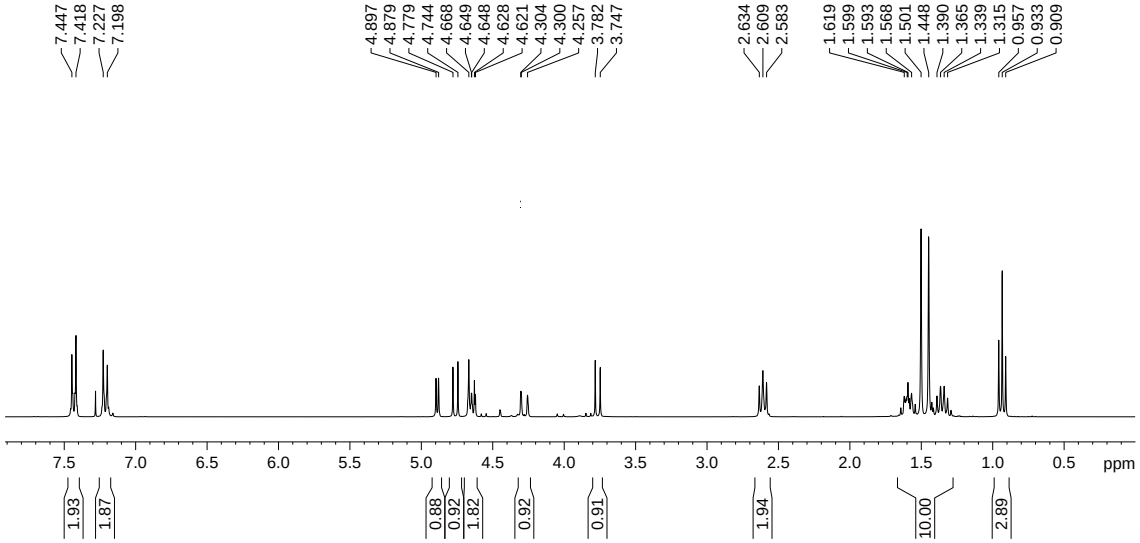


^{13}C NMR, 300 MHz, $CDCl_3$

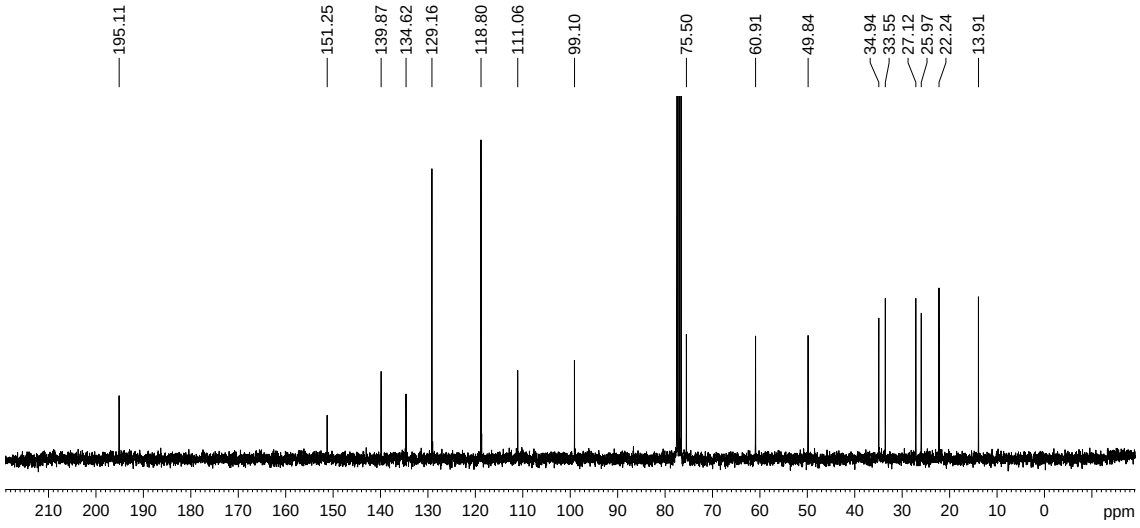


A3.8 Catalyst (84d):

^{1}H NMR, 300 MHz, $CDCl_3$

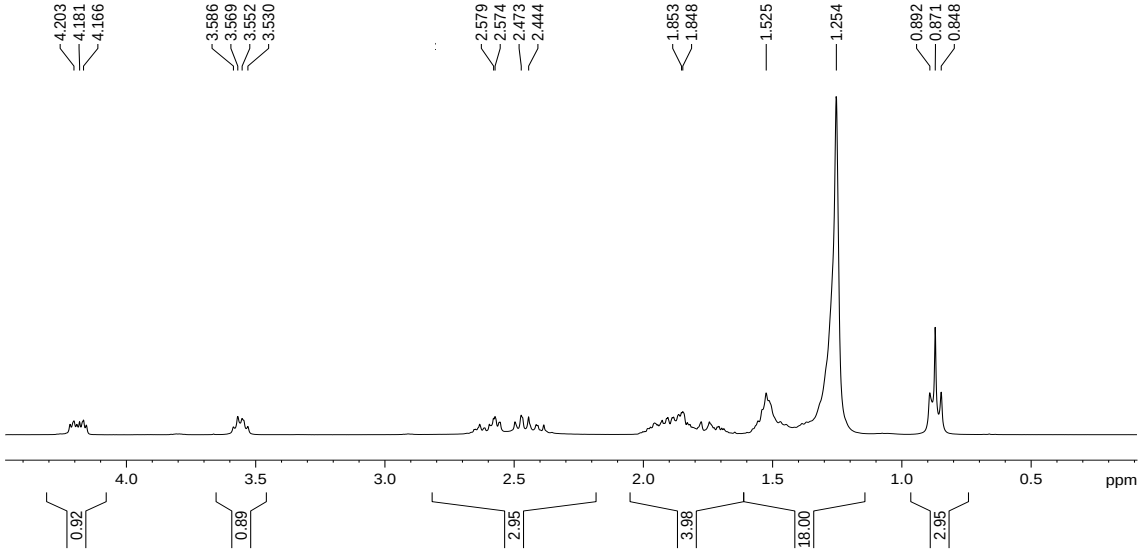


^{13}C NMR, 300 MHz, $CDCl_3$

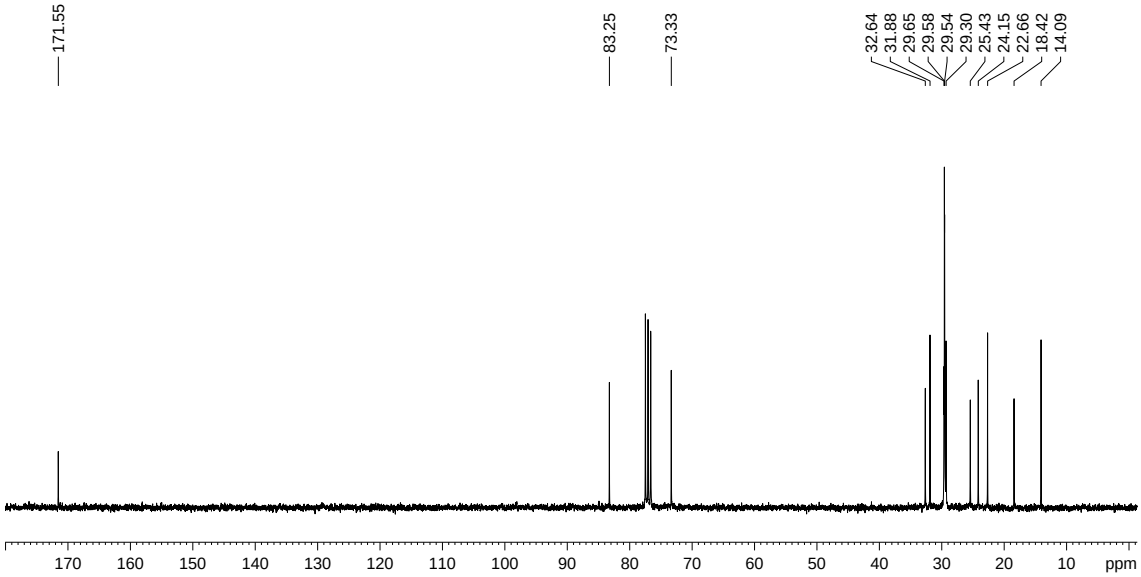


A3.9 (5*R*, 6*R*)-6-hydroxyhexadecanolide ((-)-20), chirality from (84b):

^{1}H NMR, 300 MHz, $CDCl_3$

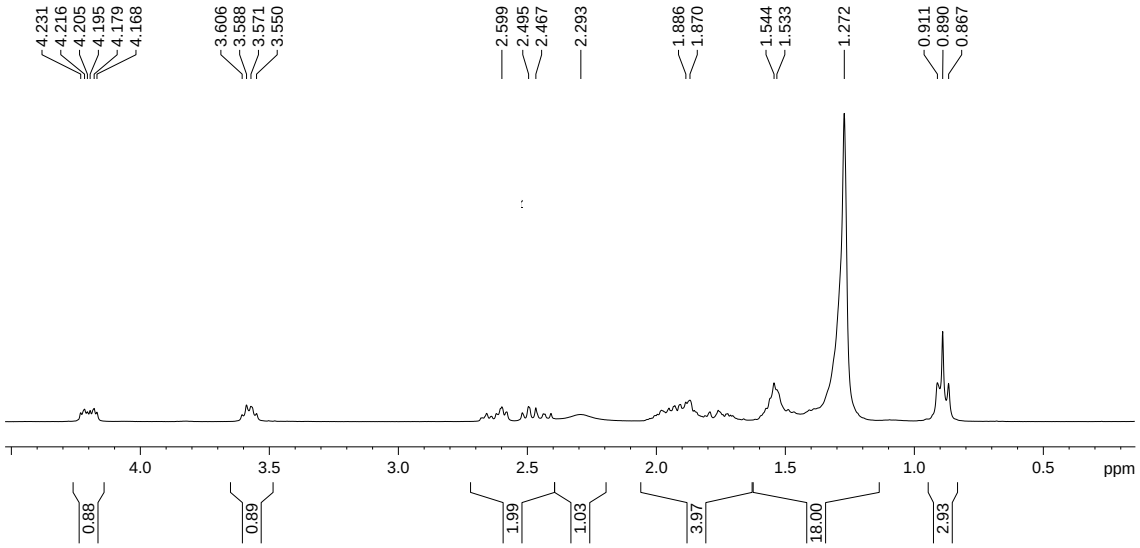


^{13}C NMR, 300 MHz, $CDCl_3$

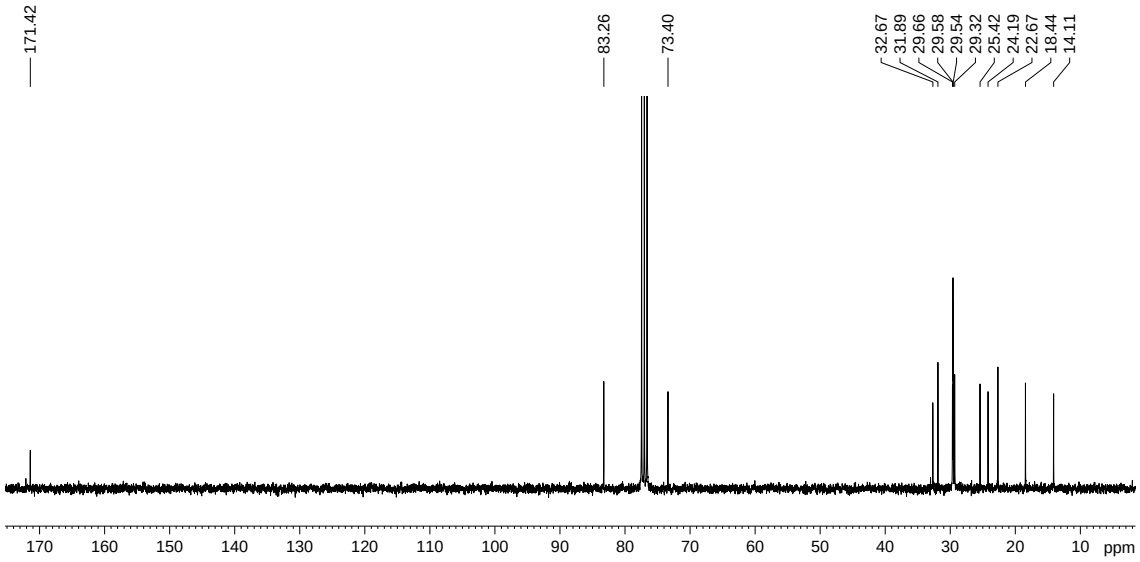


A3.10 (5*R*, 6*R*)-6-hydroxyhexadecanolide ((-)-20), chirality from (84c):

^{1}H NMR, 300 MHz, $CDCl_3$

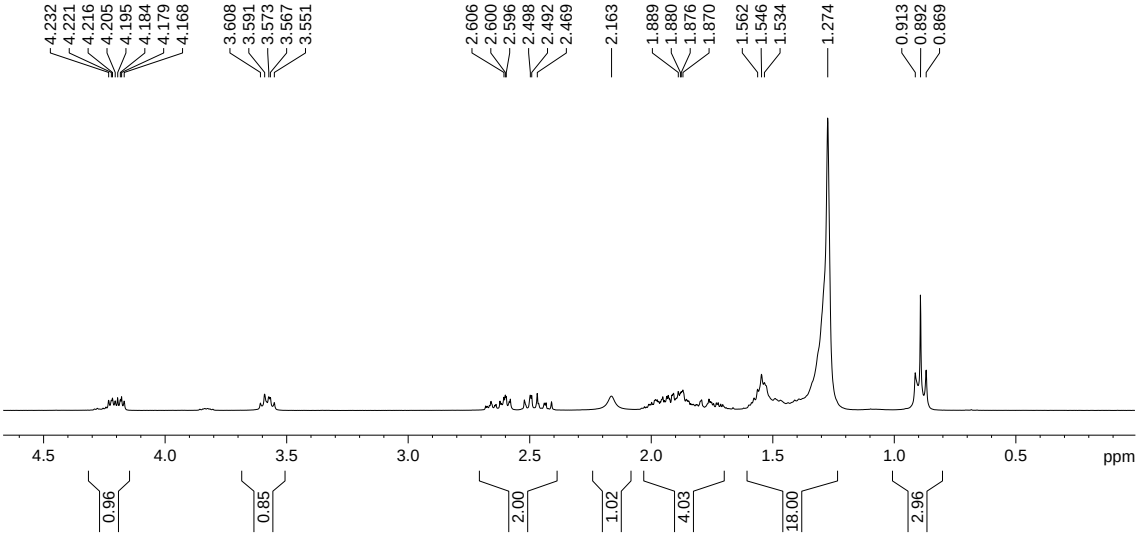


^{13}C NMR, 300 MHz, $CDCl_3$

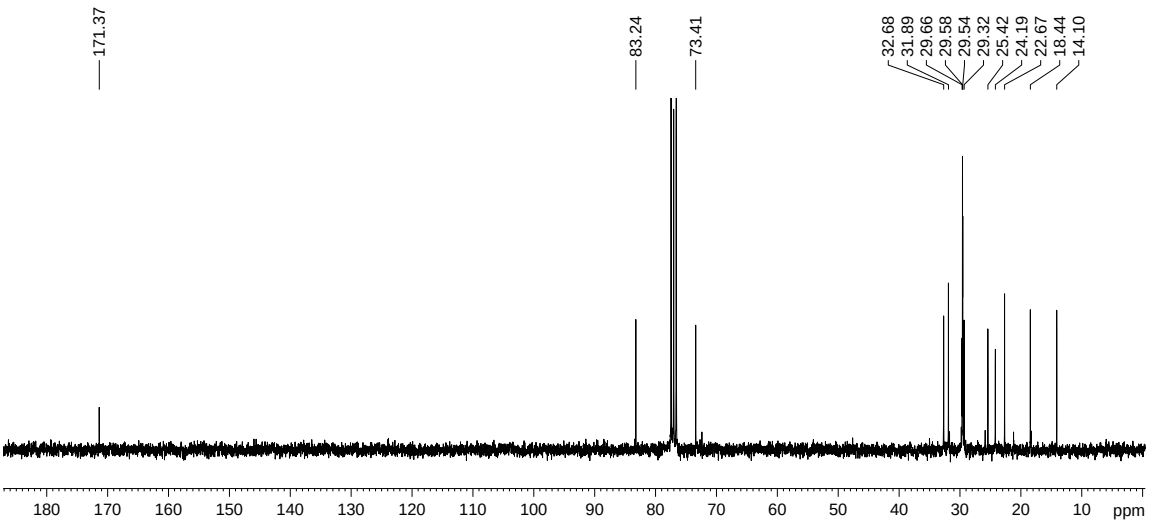


A3.11 (5*R*, 6*R*)-6-hydroxyhexadecanolide ((-)-20), chirality from (84d):

^{1}H NMR, 300 MHz, $CDCl_3$

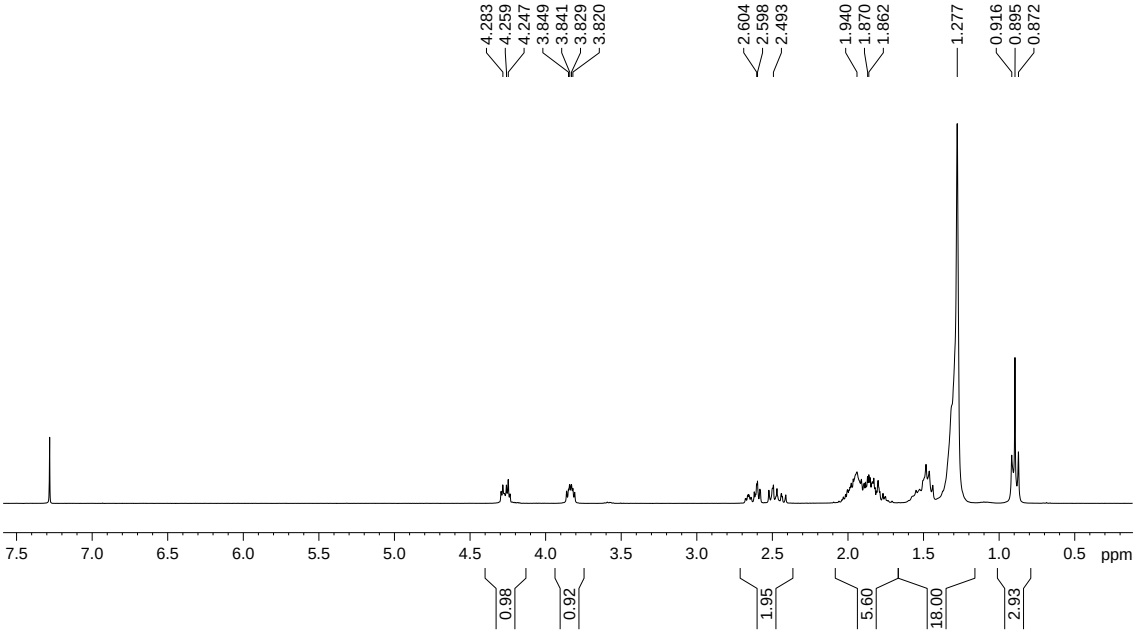


^{13}C NMR, 300 MHz, $CDCl_3$

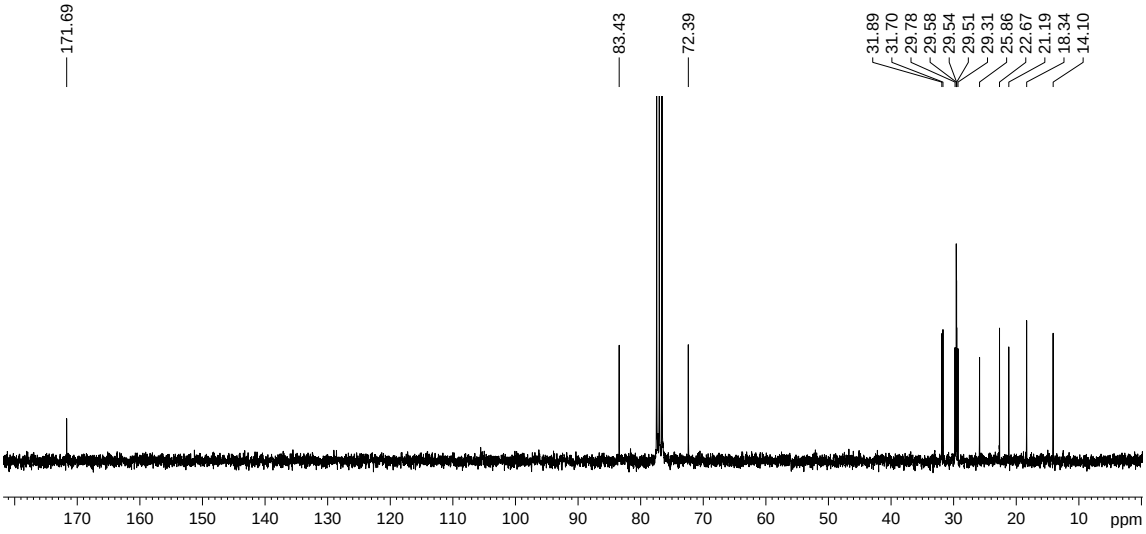


A3.12 (5*R*, 6*R*)-6-hydroxyhexadecanolide ((-)-20), chirality from L-proline:

^{1}H NMR, 300 MHz, $CDCl_3$

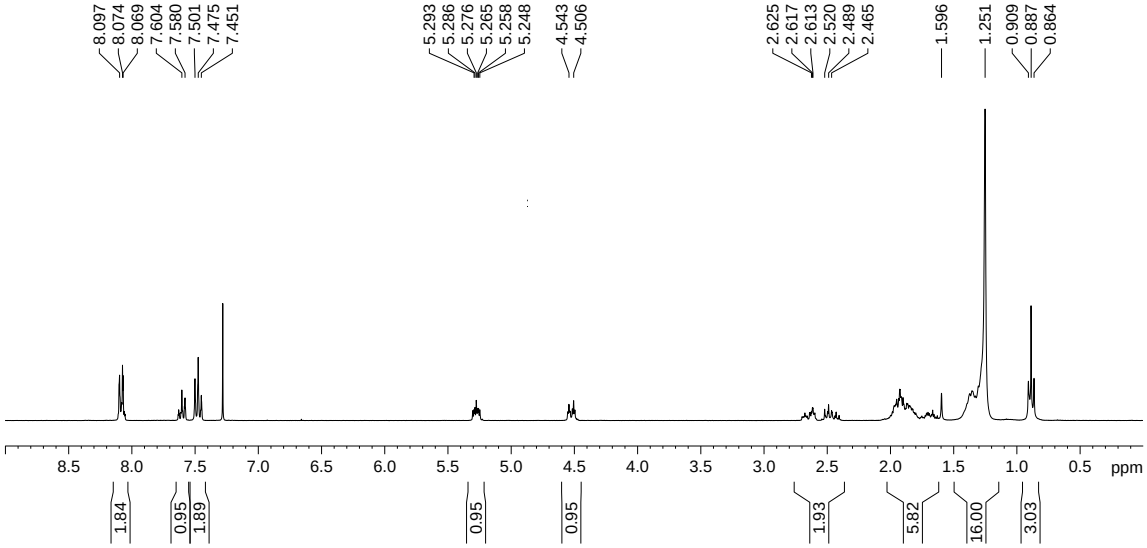


^{13}C NMR, 300 MHz, $CDCl_3$

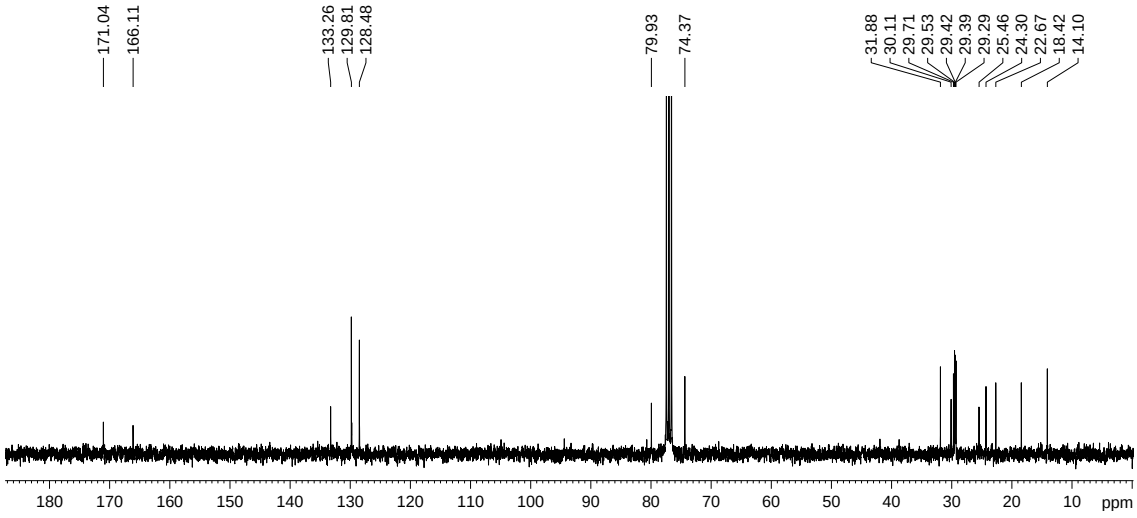


A3.13 (5*R*, 6*R*)-6-(OBz)-hexadecanolide (95), chirality from (84d):

^{1}H NMR, 300 MHz, $CDCl_3$

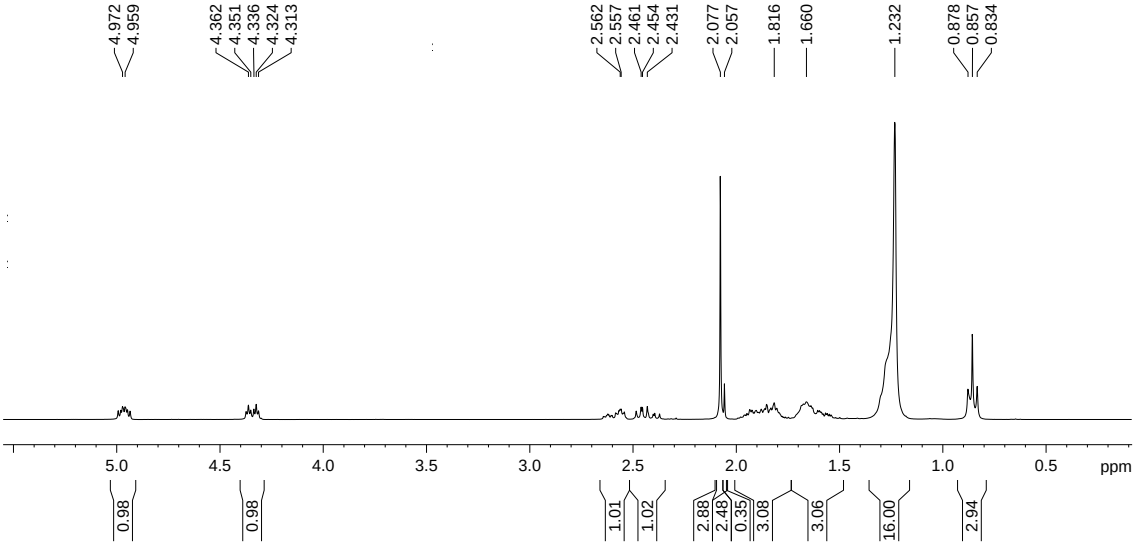


^{13}C NMR, 300 MHz, $CDCl_3$

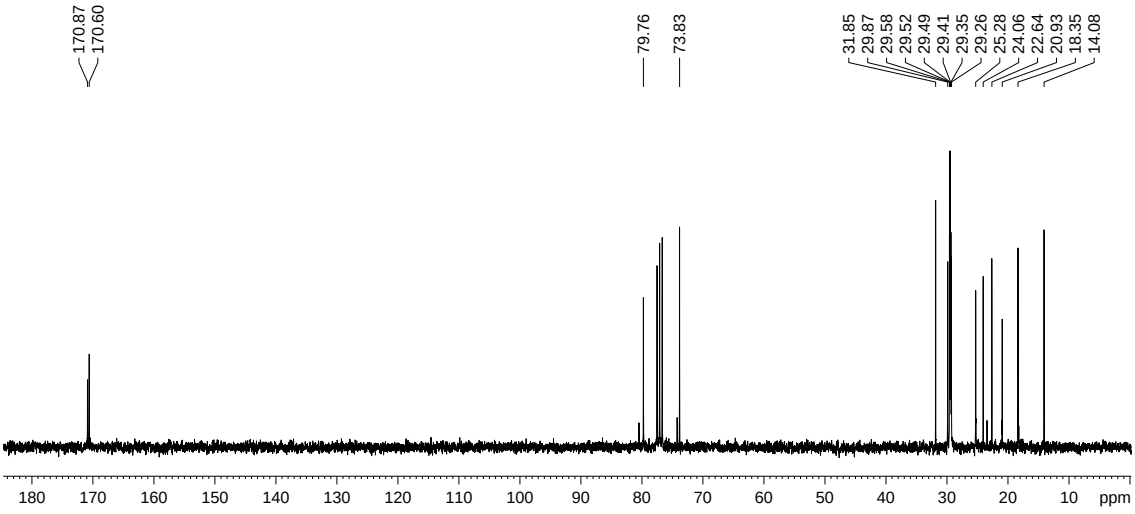


A3.14 (5*R*, 6*R*)-6-acetoxyhexadecanolide ((-)-2), chirality from (84d):

^{1}H NMR, 300 MHz, $CDCl_3$

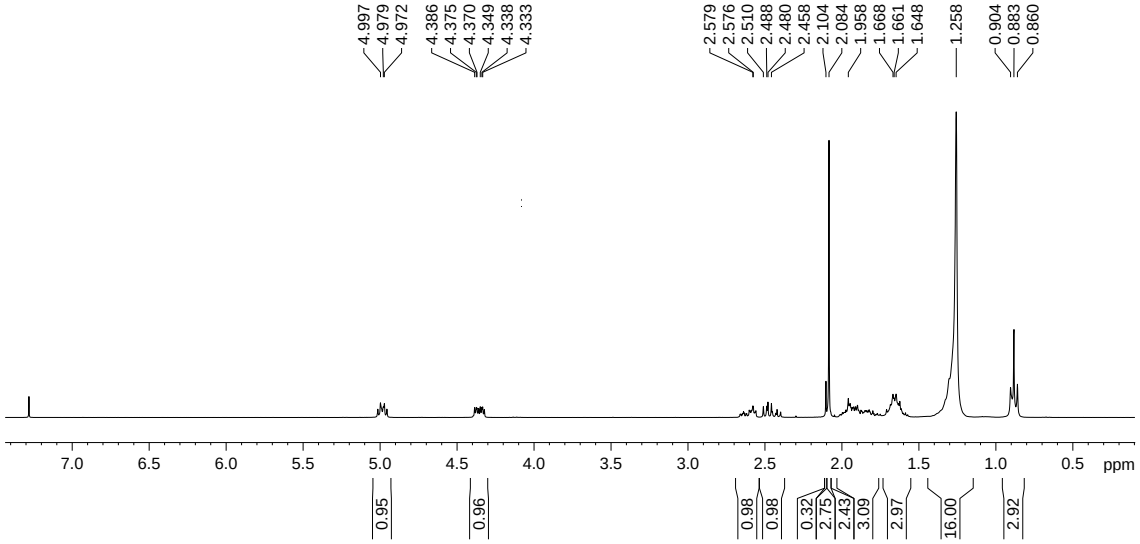


^{13}C NMR, 300 MHz, $CDCl_3$

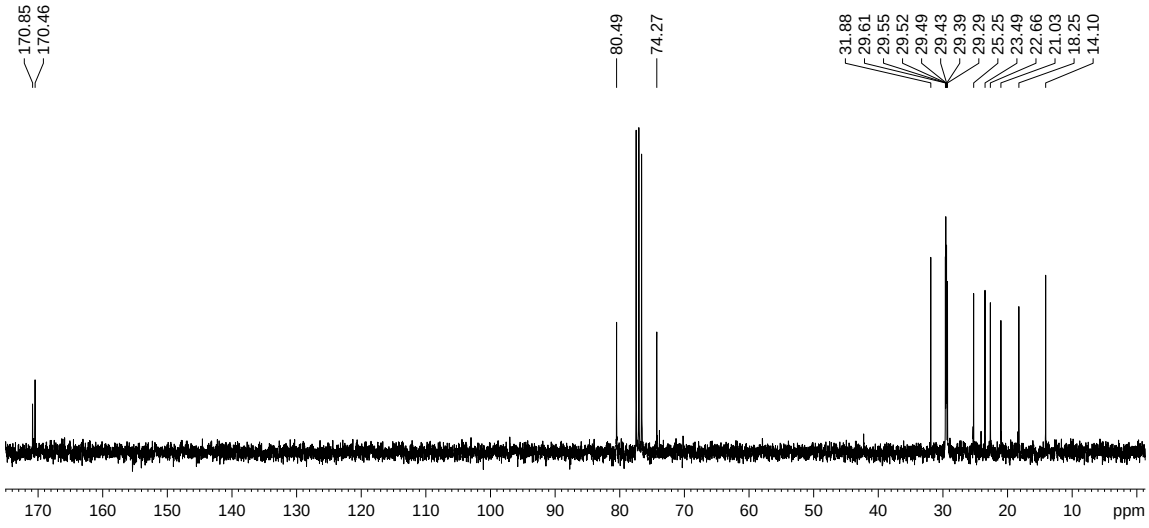


A3.15 (5*R*, 6*S*)-6-acetoxyhexadecanolide ((-)-1), chirality from (84d):

^{1}H NMR, 300 MHz, $CDCl_3$

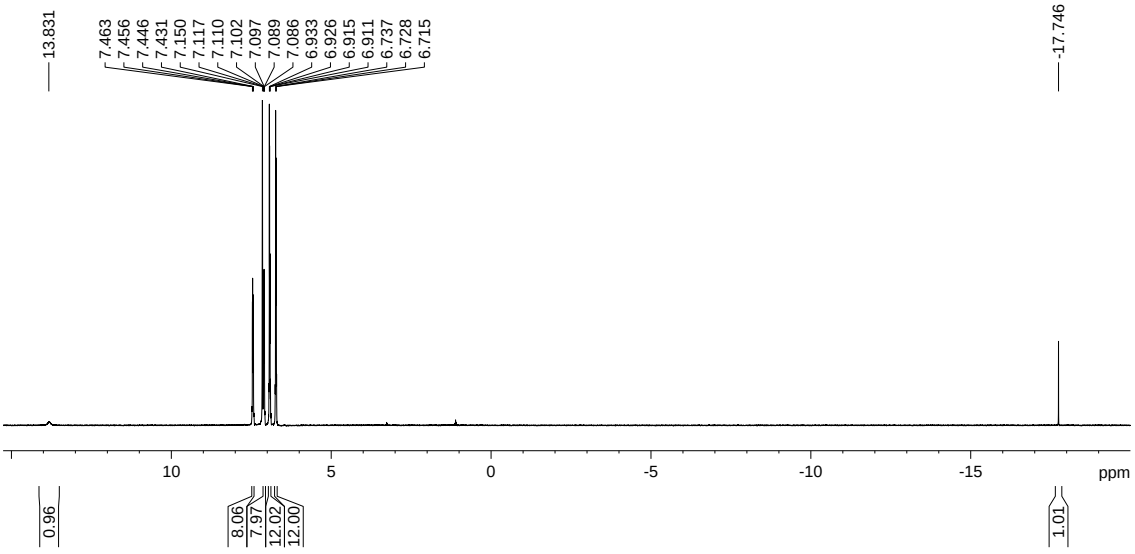


^{13}C NMR, 300 MHz, $CDCl_3$

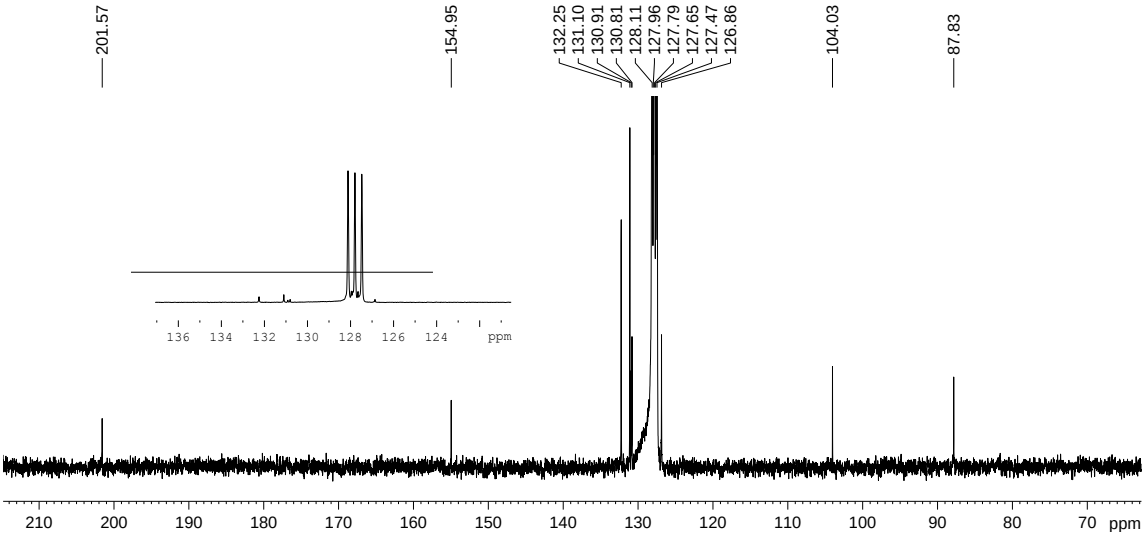


A3.16 Shvo's Catalyst (85):

^{1}Hydride NMR, 300 MHz, $CDCl_3$

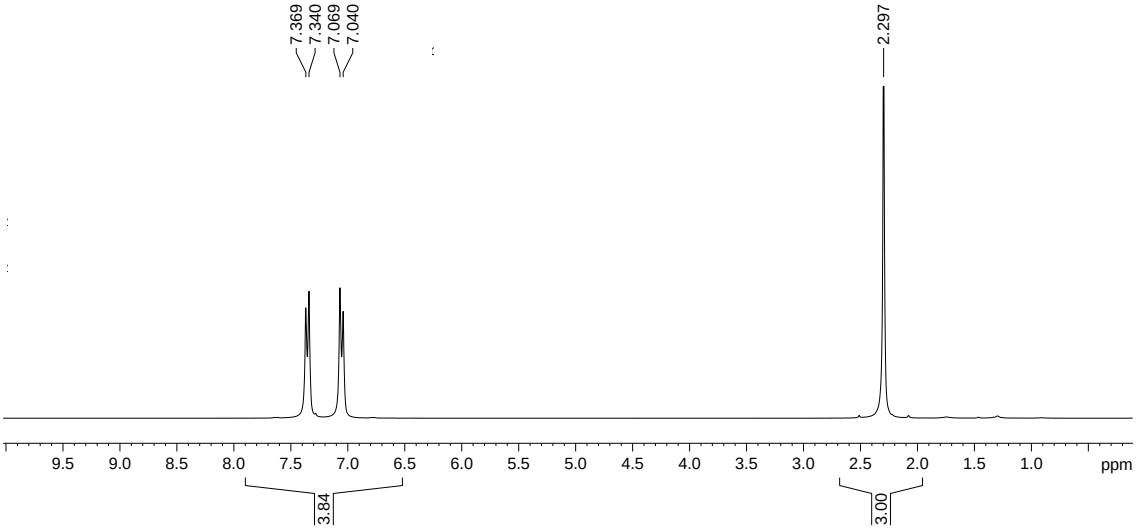


^{13}C NMR, 300 MHz, $CDCl_3$

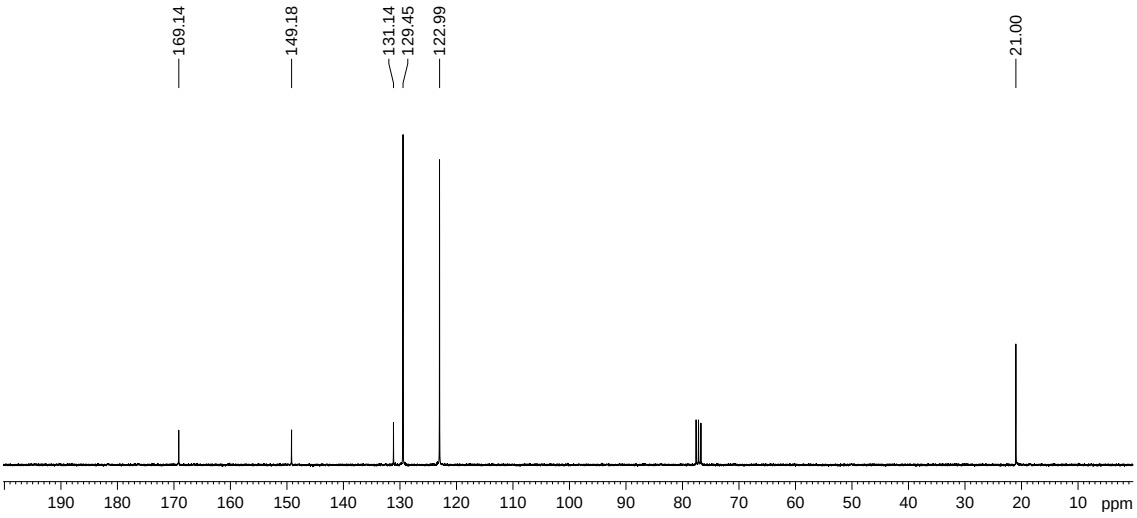


A3.17 *p*-chlorophenyl acetate (100):

^{1}H NMR, 300 MHz, $CDCl_3$

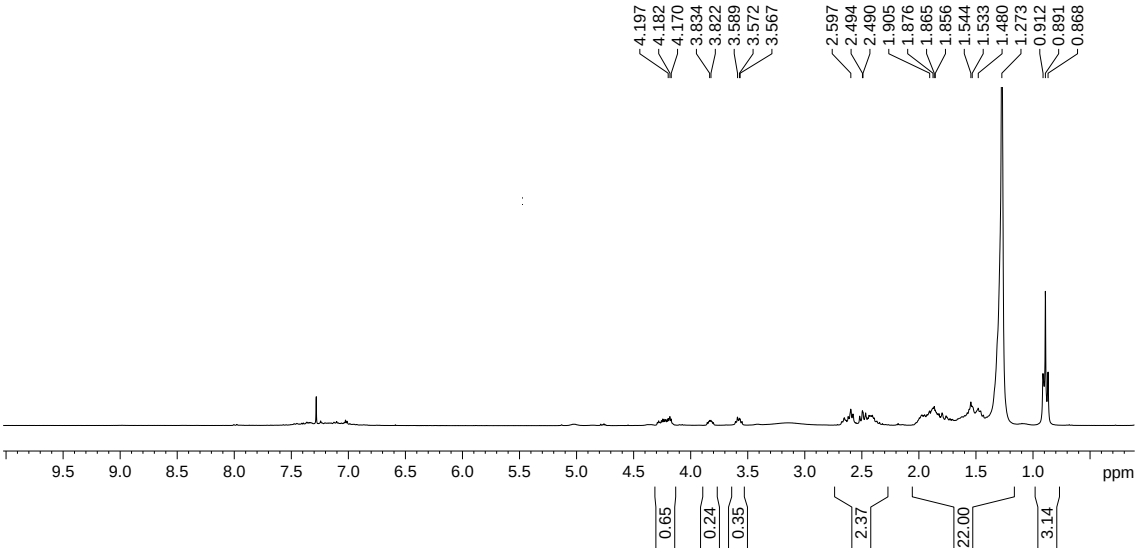


^{13}C NMR, 300 MHz, $CDCl_3$

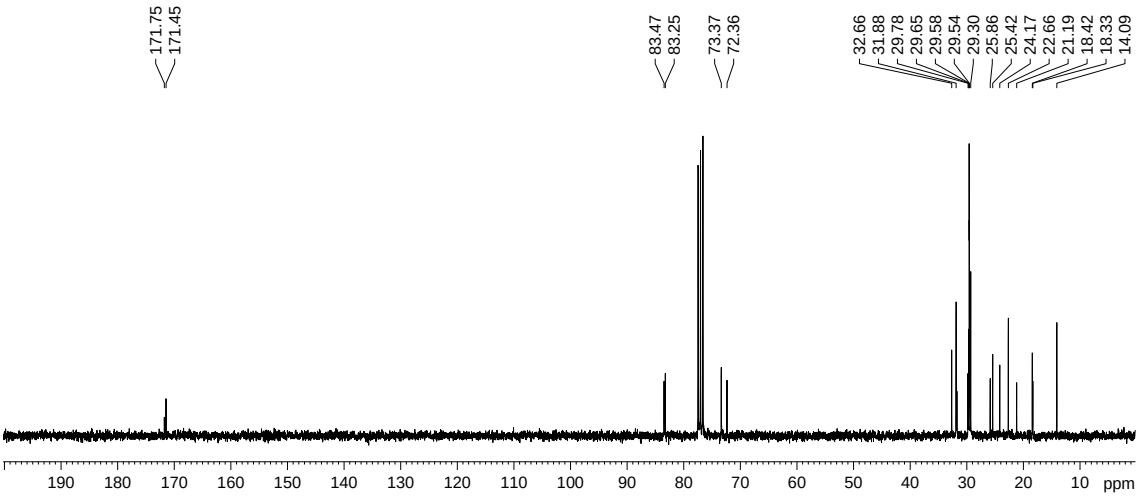


A3.18 Epimerization of ((±)-20) to ((±)-10) using Shvo`s Catalyst (85):

^{1}H NMR, 300 MHz, $CDCl_3$

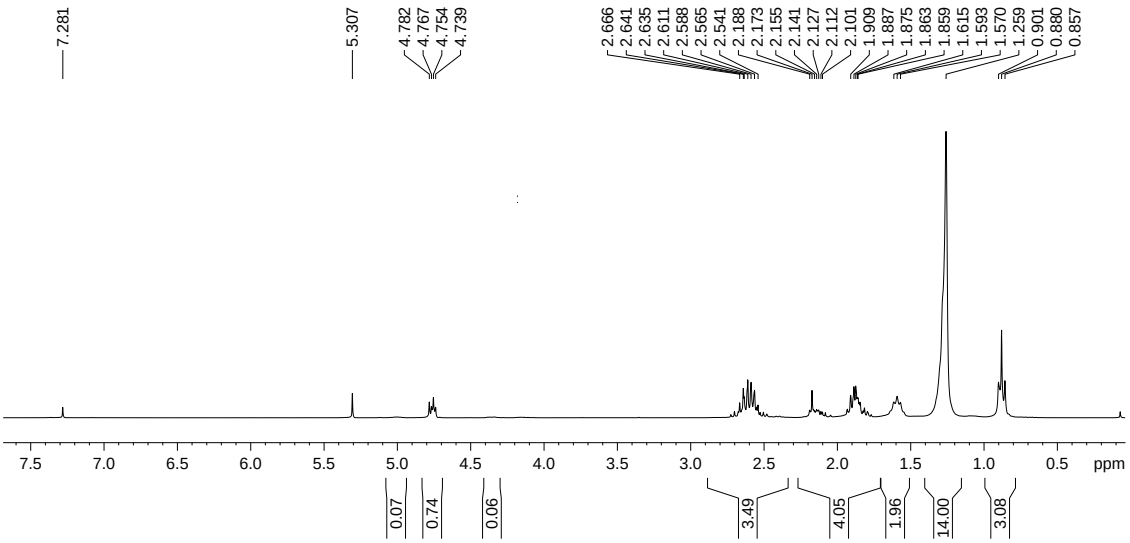


^{13}C NMR, 300 MHz, $CDCl_3$

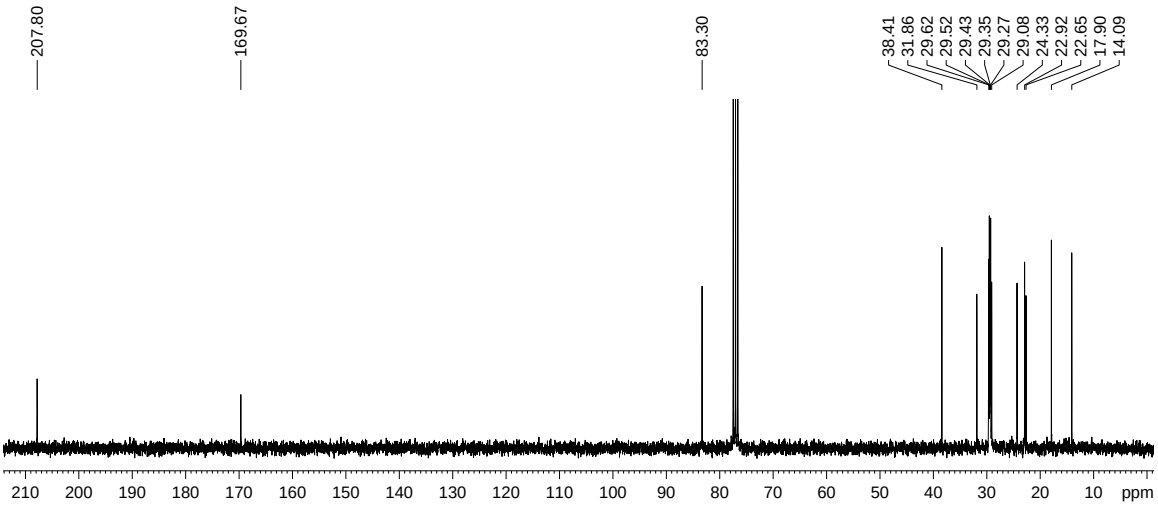


A3.19 Product from attempted dynamic kinetic transformation of ((±)-20) using vinyl acetate donor (87):

^{1}H NMR, 300 MHz, $CDCl_3$

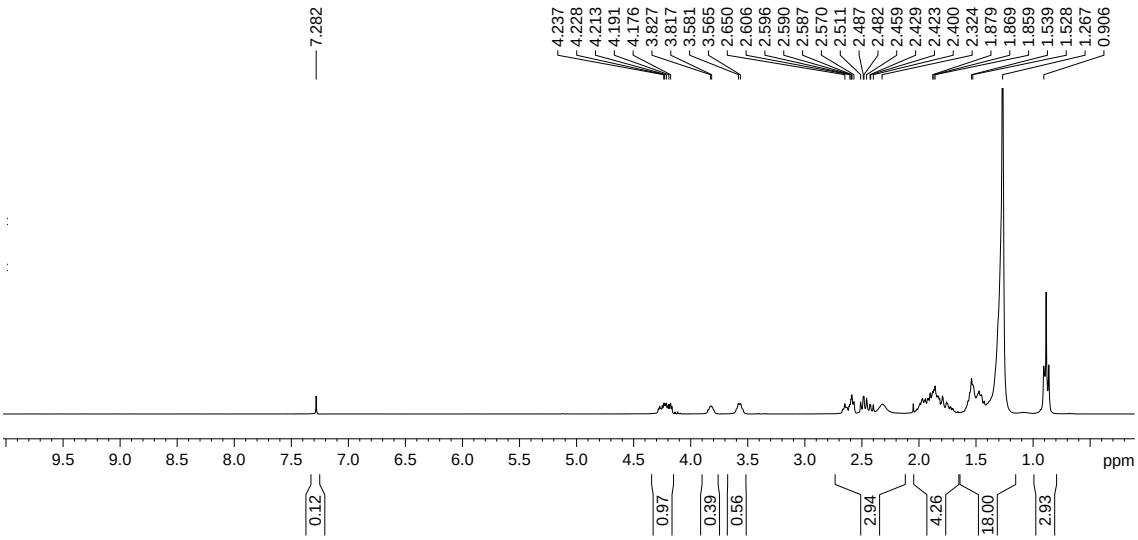


^{13}C NMR, 300 MHz, $CDCl_3$

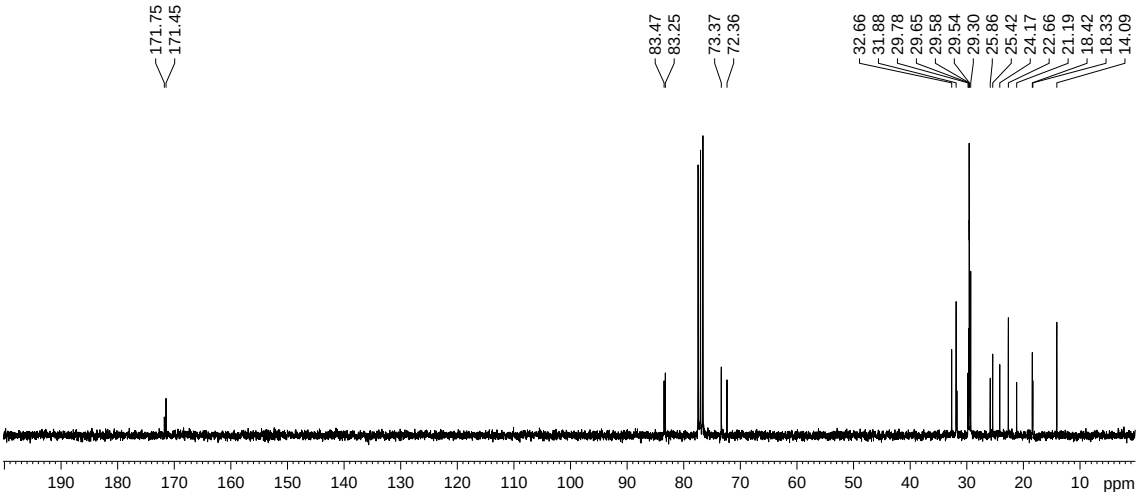


A3.20 Recovered starting material from attempted dynamic kinetic transformation of ((±)-20) using vinyl acetate donor (20 + 10):

^{1}H NMR, 300 MHz, $CDCl_3$

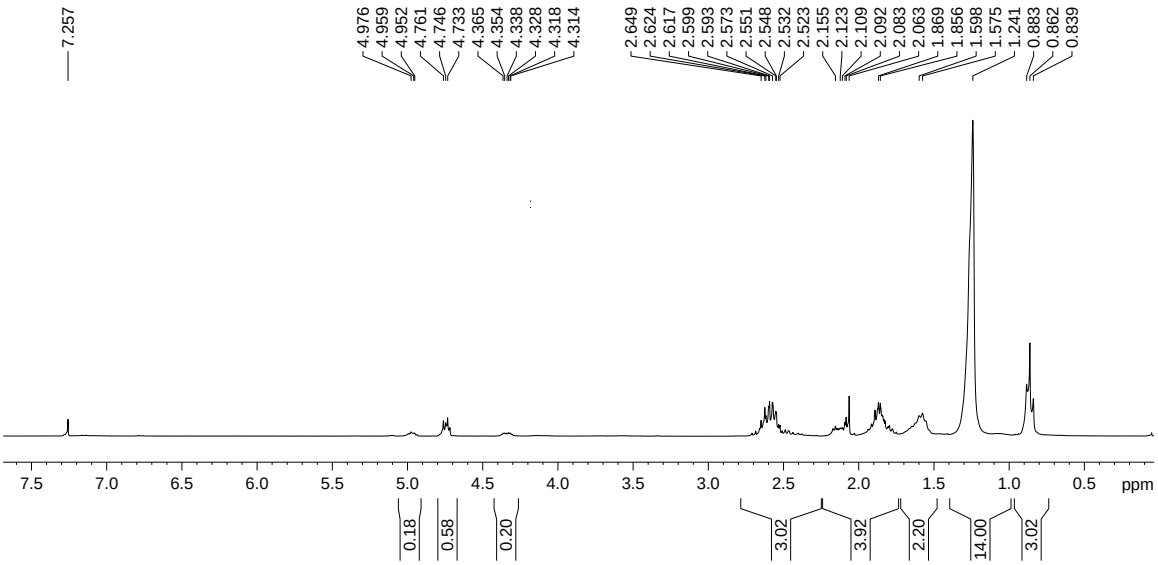


^{13}C NMR, 300 MHz, $CDCl_3$

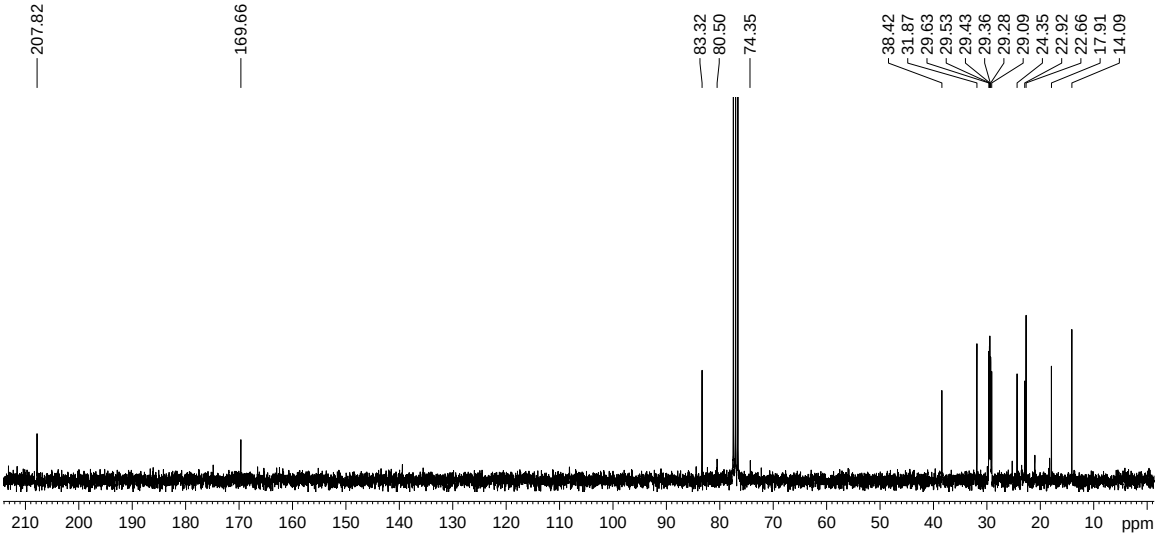


A3.21 Product from attempted dynamic kinetic transformation of ((±)-20) using (100):

^{1}H NMR, 300 MHz, $CDCl_3$



^{13}C NMR, 300 MHz, $CDCl_3$



A4.0 Raw Data for Metric Analysis

A4.1 Dawson *et al*. Synthesis[9]

Step 1: Aldol Reaction

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
$TiCl_4$	9.5	189.679	0	0.050
1-TMS-l-cyclopentene	7.9	156.29	8	0.051
undecanal	8.5	170.29	11	0.050
Product 1	13.3	254.22	16	0.052

Yield = not reported, E = 0.9, RME = 51 %, CE = 88 %

Step 2: Key Oxidation Step

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
Product 1	13.3	254.22	16	0.052
m-CPBA	10	172.57	7	0.058
KF	3	58.09	0	0.052
Product 2	11.6	270.41	16	0.043

Yield = 86 %, E = 1.3, RME = 44 %, CE = 55 %

Step 3: Acetylation

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
Product 2	5	270.41	16	0.018
Ac_2O	10	102.09	4	0.098
pyridine	9.8	79.1	5	0.124
Product 3	5.7	312.44	18	0.018

Yield = 100 %, E = 3.4, RME = 23 %, CE = 25 %

A4.2 Michaelakis *et al*. Synthesis[12c]

Step 1: Reduction of Valerolactone

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
valerolactone	4.0	100.12	5	0.0400
DIBAL-H	6.3	142.22	8	0.0440
Product 1	3.6	102.13	5	0.0352

Yield = 88 %, E = 1.8, RME = 35 %, CE = 32 %

Step 2: Wittig Reaction

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
Product 1	0.20	102.13	5	0.0020
n-BuLi	0.19	64.06	4	0.0029
Undecyltriphenylphosphonium bromide	2.4	497.48	29	0.0048
Product 2	0.42	240.42	16	0.0017

Yield = 89 %, E = 5.6, RME = 15 %, CE = 17 %

Step 3: Primary Alcohol Oxidation

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
Product 2	0.42	240.42	16	0.0017
$K_2Cr_2O_7$	0.26	294.18	0	0.0009
Product 3	0.35	254.41	16	0.0014

Yield = 80 %, E = 1.0, RME = 51 %, CE = 79 %

Step 4: Key Oxidation Step

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
Product 3	0.50	254.41	16	0.0020
K_3FeCN_6	1.9	329.24	0	0.0059
K_2CO_3	5.91	138.2	0	0.043
K_2OsO_4 $2H_2O$	0.0074	368.42	0	0.000020
Product 4	0.52	288.42	16	0.0018

Yield = 90 %, E = 15, RME = 6.2 %, CE = 92 %

Step 5: Cyclization/Acetylation

Reagent	Mass (g)	FW (g/mol)	Carbons	mol
Product 4	0.10	288.42	16	0.00035
pyridine	5.9	79.1	5	0.074
Ac_2O	1.3	102.09	4	0.012
Product 5	0.087	312.44	18	0.00028

Yield = 80 %, E = 83, RME = 1.2 %, CE = 1.2 %